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1. Briller, S. A.: *M. Clin. North America* 41:619, May, 1957.
2. Tainter, M. L.: *Bol. Asoc. méd. Puerto Rico* 47:305, Aug., 1955.

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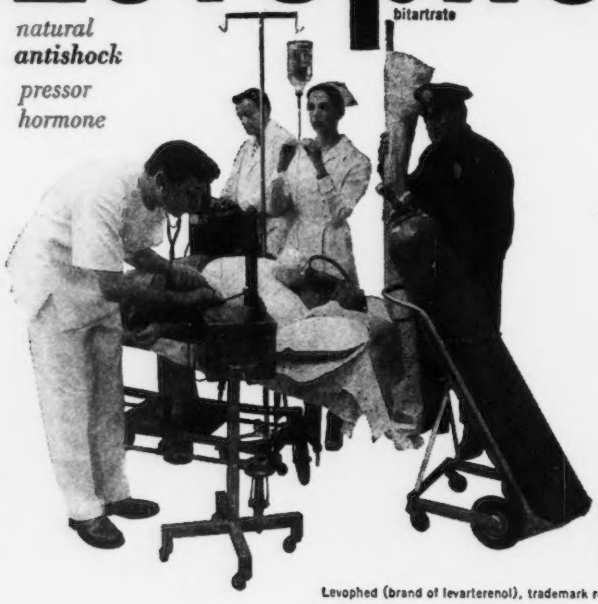

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Editorial

A Survey of Cardiac Electrophysiology

THE UNDERSTANDING of the electric properties and behavior of the cellular aggregates of the heart, and the projection of their effects through body tissues to the surface of the organism has yielded a complex body of information that is the sum total of labors contributed by physiologists, physical chemists, biophysicists, electrical engineers, and clinical investigators. It is apparent that the factual observations and the theoretical analysis derived therefrom are likely to replace to a considerable degree the empirical approach of clinical electrocardiography.[1] This brief review intends to scan superficially some basic advances made in recent years. It seems reasonable to single out 4 investigative areas of general interest in this field.

A. The Significance of Transcellular Potential Gradients

The recording of intracellular events by microelectrodes has yielded information similar to and in a purely qualitative sense may be considered an extension of the previously reported analyses of monophasic injury effects. The true intracellular placement of an electrode, however, has allowed a more precise analysis of the events associated with excitation and recovery and has provided us with a new approach. Much of this information has been of a descriptive kind and the theoretical interpretations have largely been translations of the neurophysiologists' concept of nerve action. The structural complexity of the myocardial fiber as revealed, for instance, by the electron microscope suggests that perhaps the concepts of a single membrane barrier to electrolyte transport might not be sufficiently broad to encompass the possible interaction of microscopic and submicroscopic structures.

It appears that the newer anatomic studies will have a considerable bearing on further interpretations of the nature of the electrical events of cardiac fibers. Electron microscopic studies have now demonstrated the cellular architecture of cardiac muscle and seemed to have answered the long controversy on the syncytial nature of the heart. The myocardium is now considered composed of individual cells joined end to end at the intercalated disks.[2] These are double membranes placed crosswise to the fiber but continuous with the sarcolemmal sheath encasing a fibril. Such studies have also demonstrated the presence of many additional "membranes": double layers which enclose the nucleus, the sarcosomes (mitochondria), and possibly other subcellular structures. The contractile myofibrils within the cell are in intimate contact with canal-like interspaces lined by membranes and filled with endoplasmic reticulum.[3] They have been considered to act as an "intracellular circulatory system" with access to the extracellular surroundings, or as "intracellular conductors" facilitating excitation and allowing for both longitudinal and lateral conduction. The myofibrils themselves extend across

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the entire cell from one intercalated disk to the next. Their point of insertion there gives this region special significance, particularly since the disk regions have been shown to possess considerable metabolic activity.[4] The capacitance and resistance of such a boundary should be of interest, and the spread of excitation across it (perhaps in saltatory fashion) raises a number of speculative possibilities.

In view of these intracellular complexities the observation of electrical alternans from one cell or the presence of complete dysrhythmia within a fiber in ventricular fibrillation, though not explained, becomes less puzzling. Obviously, the recording of potentials from somewhere within this complex system yields data that one cannot simply relate to the events occurring at a simple membrane of the kind that Bernstein visualized. A multiple steplike process, much more closely related to a mathematic model suggested by Polissar seems somewhat more appropriate.[5]

There is good agreement, however, between experimental data of all excitable tissues so studied, including the heart, and calculations made many years ago on the magnitude of bioelectric potentials which were based upon the concept of diffusion potentials at liquid boundaries. This suggests strongly that unequal diffusion of electrolytes may indeed play an important role in the maintenance of a resting steady state within the fiber. Whether the recorded potential gradient is the result of ionic shifts or its cause is of less concern than the observations that the presence of interdependent ionic fluxes which may be implicated in the general processes of excitation appears to hold for cardiac muscle as well, though in a form modified by as yet unknown metabolic or enzymatic characteristics of that tissue.

As an example, the direct dependence of cardiac resting potential on extracellular potassium concentration, well demonstrated for nerve fibers and other tissues,[6] cannot be demonstrated as easily for cardiac fibers.[7] As in other tissues, the establishment of a positive intracellular Na^+ balance at the height of excitation, and subsequent movement of this ion against the electrochemical gradient, implies the intracellular formation of a metabolic "pump" substance, NaP^+. Its presence needed to explain the strong outward sodium current that initiates return to the steady resting state is based on circumstantial evidence but is required if our present understanding of excitatory processes is to be retained. Changes in permeability with molecular rearrangement of the membrane or membranes, ionic flux, and metabolic activity in forming pump substances are all interdependent. They result in a net electric current, the sum of the individual ionic fluxes multiplied by their charge number. It seems obvious that a further insight into these complex mechanisms will advance our understanding of basic cardiac properties such as pacemaker function, excitability, and refractoriness, and will redirect our interpretation of the action of pharmacologic agents into terms of molecular and ionic interactions.

The sodium pump is not peculiar to excitatory tissues alone. Transcellular potentials of renal cells have been measured, and the need of a sodium pump for an active transport of Na^+ from cell to peritubular fluid and in consequence inward movement of Na^+ from the proximal and distal tubules into the cells has been postulated.[8] In the distal tubules an additional coupled ionic pump which reabsorbs sodium in exchange for hydrogen or potassium has been implied. Sulfhydryl enzymes are vital to such sodium transport systems and are inactivated by mercurial diuretics, which thus interfere with the operation of the sodium pump. Here is an example of the overlapping of biologic interests with answers likely to appear from unexpected corners.

Several mathematical expressions are available that define external potentials at the cell surface as well as the summed potential of all cardiac cells in terms of membrane currents using differential equations in part based on the theory of transmission of electric currents through cables.[9] In general, one can state that the surface potentials of a heart submerged in a volume conductor are proportional to the

second derivative of the sum of all transcellular currents, and that in turn the configuration, though not the magnitude, of the cellular potential-time sequence can be predicted from surface records.[7] These are the first halting steps of a very much needed correlation. When carried further these experimentally observed interrelationships amplify some of the theoretic concepts of the T wave and connect directly with the notion of the ventricular gradient. Differences in the length of the excitatory period upon which the gradient concept is based have now been demonstrated on the cellular level. Changes in sign of T are likely to be determined by such differences, while the magnitude of this deflection appears to be a function of the rate of return of the transcellular potential from the excited to the resting steady state condition.

B. The Equivalent Dipole and the Dipole Moment

In a conducting medium, the potential difference existing at the boundary between resting and excited fibers may be expressed as an electric dipole with a positive source and a negative sink. Such an electric "doublet" must be considered a singularity—source and sink cannot be treated separately. It causes an electric field throughout the medium that surrounds the muscle, and its strength is proportional to the polarization of the fiber. The strength is termed the "dipole moment" and characterizes the doublet. It is the product of charge times the distance between source and sink. The apparent movement of this doublet from cell to cell, corresponding to the successive and transient changes in fiber permeability, is reflected by a change in the surrounding electric field, which in turn may be traced as the path of the action potential. Its successive arrival at various points of the myocardium and therefore the path of the "impulse" can be recorded by small contiguous bipolar electrodes, or by the so-called "unipolar" electrode technic of Lewis. Both methods give comparable results. The former signals the arrival of the impulse subjacent to the electrode placement by a sharp "intrinsic" deflection, and may be considered to represent accurately the onset of local excitatory processes.[10] The intrinsic deflection of a unipolar lead is more easily subjected to influences of remote areas, and therefore when the 2 types of intrinsic deflections are compared, differences between them may become apparent. In spite of the apparent superiority of bipolar recordings, the unipolar intrinsic deflection has served remarkably well in the past in attempts to map grossly the time action course of excitation through and over cardiac musculature. However, since the onset of the unipolar intrinsic deflection does not always coincide with the arrival of the impulse underneath the exploring electrode, the use of the "intrinsicoid" deflection in precordial leads has little more than empiric value, and may largely be taken as a vectorial representation of excitation produced by large muscle segments.

The doublet concept of excitation of individual fibers may be expanded, leading to the experimental approach whereby the sum of all individual electromotive forces arising within the cardiac fibers may be considered as a single equivalent dipole for each instance of time. Essentially this approach originated with Einthoven's concept of "manifest" potentials, size and magnitudes of which he calculated for the frontal plane from their vectorial representation on the chest. It is a powerful intellectual device, which has been expanded and refined, and has led to various general theories on heart-vector projections.[11] Its validity in man and in appropriate models has been claimed irrefutable by the so-called cancellation technic, whereby exact mirror images obtained over opposite areas of the chest are cancelled by appropriate bridge circuits.[12] Records obtained with artificial dipoles placed in models and cadavers have yielded a large body of information in support of the heart vector concept as the only accurate approach to certain theoretical and clinical interpretations of the electrocardiogram. To the extent that cancellation is incomplete, the single equivalent dipole concept

is not fully applicable; perhaps several dipoles might be considered, and the use of special selective exploratory chest leads should find their usefulness under those circumstances. Evidence has been presented that this situation is more likely to occur in abnormal hearts than in subjects without cardiac disease.[13]

The orientation and magnitude of a single resultant dipole of the heart can be calculated from appropriate surface leads in turn. A mathematical treatment and limited experimental observations on the strength of the dipole moment itself existing between the equivalent source and sink are available. It is not surprising that this value describing the lumped dipole source is directly proportional to the total muscle mass of the heart.[14]

This area of electrophysiologic research, always an explosive field, has recently entered a new phase: In addition to the possibility that the surface records cannot under all circumstances be expressed as the manifestation of a single dipole, there is now some doubt that mirror patterns and cancellation can even be considered a proof for the equivalent heart dipole concept[15]—an ugly specter for those interested in creating intellectual order from an exceedingly complex biophysical system.

C. The Spread of Excitation through Cardiac Tissue

An elaborate mapping of the time course of the onset of excitation through the heart, particularly over the ventricular musculature (QRS), has supported many of the earlier measurements of Lewis and Wilson. In general, the spread is normal (perpendicular) to the endocardial surface. Since the spread of excitation over a fiber is likely to be lengthwise, however, rather than across, a more complex picture is needed to supplement statements on the general order of transmural excitation. The assumption of an interlacing network of islets separately excited by more or less deeply penetrating Purkinje fibers, occasionally even causing reversal of the excitatory spread within the myocardium, seems now well supported. Longitudinal spread, as contrasted to excitation from within outward, has been demonstrated for papillary muscle, part of the septum, and for hypertrophied muscle over segments of the ventricular outflow tract. Such a separation into various units, which are depolarized independently, may cause the emergence of the excitatory process at the epicardial surface over several areas simultaneously, and for short distances longitudinal spread may occur here as well. This appears no more than a modification of the earlier observations of Lewis, although Schaefer's epicardial source-point analysis, "Quellpunkt," departs fairly drastically from the classic concept.[16]

The process of recovery does not lend itself as easily to such a segmental analysis. The first major departure from purely empirical descriptions of the T wave was introduced by the demonstration that the measurements of the mean, e.g., two dimensional time integrated, direction of electromotive forces of the heart yielded information on the rate of recovery. If the duration of the excitatory state is identical throughout the ventricular musculature, the externally measured action potential integrates to zero over the full cardiac cycle, and consequently a lack of uniformity in the duration of the excitatory state produces residual electric forces that are reflected in certain changes of the T deflection. Cellular potentials have tended to confirm this concept and have added the need for some additional considerations: (a) several, apparently metabolic, steps are involved in the recovery process, and (b) uniform changes in the *rate* of recovery should alter the surface T wave, independent of the differences in the duration of the excitatory processes. Recovery has been assumed to follow excitation as a consequence of the interior mechanisms of the fiber. A curious phenomenon has recently been rediscovered by which it appears that repolarization can also be induced externally by anodal stimulation.[17] Since a repolarized, resting cardiac segment may act as an anode, it is possible to visualize recovery as a propagated process. The significance of these observations needs to be determined, but it is obvious that a further analysis of the time sequence of

transcellular potential gradients might well provide new information on the nature of T-wave changes.

D. The Analysis of Surface Leads

The surface representation of the electric activity of the heart is influenced by the electric characteristics of body tissues and by the effect of a finite boundary, the chest wall. The electric inhomogeneity of tissues surrounding the heart appear to be relatively inconsequential except for the presence of low resistance (increased conductivity) existing within the chambers of the heart itself. This factor, attributed to a shunting action of the blood within the heart, tends to decrease the external surface potentials, and its effect should be magnified under certain pathologic conditions. It may also tend to concentrate the electric field within the heart, thus strengthening the concept of an equivalent dipole.

The effects of the thoracic wall on the distribution of electric potentials over its surface have not been fully analyzed, but a detailed treatment for relatively simple geometric boundaries is available and offers a solution by the "image system" proposed for electric networks many years ago.[18] A more precise 3-dimensional solution appears extremely laborious but is needed if one is to evaluate the details of surface potentials, although the concept of lead vectors as now developed is independent of such influences. With the exception of the position of the zero potential line, which in a finite medium is *not* located at the transverse axis of the true dipole, it is unlikely that body inhomogeneity and boundary effect invalidate the general conclusions derived from studies that considered the tissues surrounding the heart homogeneous and the boundary infinite.

The magnitude and spatial direction of the equivalent dipole heart vector for each instance of time can, of course, like any other vector force be expressed in terms of its three orthogonal components. Any of the three components will influence a surface lead, depending on its spatial orientation with respect to these components, times a coefficient that describes the reaction of the lead to the cardiac vector forces and that involves the external modifying factors mentioned above. These coefficients may in turn be considered components of another vector force, the lead vector. The performance of a given lead is described fully by the product of the lead vector and the vector that represents the equivalent dipole of the heart.[19] Considerations of this kind have led to the description of truly orthogonal lead systems, which have been developed either by the use of model experiments with artificial dipoles,[20] or by the lead-field concept, which allows the prediction of orthogonal leads through the use of a hydraulic analog based on Helmholtz' reciprocity theorem.[21] The painstaking and laborious efforts directed toward these ends by many investigators have resulted in several "orthogonal systems" as a basis for vectorcardiography that are almost interchangeable by clinical standards. These analyses explain the incongruities of the present popular empiric vectorcardiographic technics.

The concept which assumes that the electric events occurring during the cardiac cycle can be represented by a single dipole, and that its magnitude and direction can be analyzed from surface records, has relegated the unipolar precordial leads into a position similar to the extremity leads. The single dipole concept is an extremely useful tool, but it still represents oversimplification. It does not appear generally applicable under all circumstances and to the extent that it is invalid so are the systems of vector electrocardiography that are squarely based upon it. It seems reasonable, moreover, from the general equation describing the potential variations in a spherical conductor, as well as from the lead-field concept that certain precordial leads or certain parts of a precordial record are more sensitive to voltages generated in close proximity to such leads than to those arising at a distance from it. In the case of multiple dipoles, anterior chest leads may be essential in order to obtain a reasonably complete surface analysis of intracardiac events. The use

of supplementary leads of this kind, so useful in clinical electrocardiography, appears justified on theoretic grounds.

HANS H. HECHT

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For all the fibers in the walls and in the inclosure are circular, as they are in a Sphincter, but those which are in the tendons stretched out in length, are crooked; so it comes to pass that when all the fibers are contracted, it happens that the top is brought to the bottom by the tendons, and the walls are inclosed in a round, and the heart is contracted every way, and the ventricles strengthned. Wherefore since the action of it is contraction, we must needs imagine that the function of it is to thrust blood out into the arteries.—WILLIAM HARVEY. *De Motu Cordis*, 1628.

Fibrinolytic (Plasmin) Therapy of Experimental Coronary Thrombi with Alteration of the Evolution of Myocardial Infarction

By PAUL RUEGSEGGER, M.D., IRWIN NYDICK, M.D., ROBERT C. HUTTER, M.D., ALVIN H. FREIMAN, M.D., NILS U. BANG, M.D., EUGENE E. CLIFFTON, M.D., AND JOHN S. LADUE, M.D.

To explore the possibilities of fibrinolytic therapy of coronary thrombosis, experimental studies were carried out to document lysis of coronary thrombi and to investigate the effect of fibrinolytic blood upon myocardial infarction. Serum-induced coronary thrombi were produced by a new technic and were followed by serial coronary arteriography. Control animals were compared to animals in which significant fibrinolytic activity had been induced by systemic infusions of plasmin. Tissue studies suggest that plasmin may change the evolution of early infarction. Whether these changes will ultimately result in salvage of ischemic tissue will be determined by studies now in progress.

RESTORATION of coronary circulation by dissolution of an obstructing thrombus could change the clinical course of myocardial infarction. Human plasmin (fibrinolysin) is an enzyme that has been shown to be effective in the dissolution of clots in peripheral vessels.[1-6] No data relative to the action of plasmin on experimental or clinical coronary thrombi have been reported.

In this first report the method of producing intracoronary thrombi in dogs and of documenting their presence and size by direct serial arteriography will be described. It will be shown by these same objective criteria that these thrombi can be lysed by plasmin (fibrinolysin) in adequate dosage. The effect of the fibrinolytic state and restoration of coronary blood flow upon the histologic structure of early infarction will be discussed.

METHODS AND MATERIALS

Adult mongrel dogs weighing 15 to 25 Kg. were anesthetized with intravenous sodium pentobarbital (25 mg./Kg.) and placed in a right lateral position on the operating table. Ventilation was maintained by a Harvard respirator pump through an endotracheal tube with a tidal volume of 150 to 300 ml. at a rate of 12 per minute. The heart was exposed by precordial fenestration, which included resection of 2 rib segments (fig. 1). The pericardial sac was opened and sutured to the margins of the thoracotomy opening. Cyanosis and overbreathing with respiratory alkalosis were avoided by adjusting the tidal volume for each animal to maintain the blood pH at 7.2 to 7.35. The heart action was kept under continuous electrocardiographic surveillance. To prevent ventricular fibrillation or other paroxysmal arrhythmias, premature contractions were treated with 50 to 100 mg. of procaine amide intravenously, and 5 to 10 mEq. of potassium chloride was added to the intravenous or intracoronary infusion. Drying of the heart surface was minimized by saline irrigation and covering the chest opening with a transparent plastic sheet.

A tiny proximal side branch of the left anterior descending coronary artery was dissected free and a no. 160 polyethylene catheter inserted into it. Slow infusion of 5 per cent glucose solution in saline with a constant infusion pump assured patency of this system up to 18 hours and permitted serial coronary arteriography through this catheter. Delineation of the coronary tree was obtained by injection of a radiopaque mixture of 50 per cent sodium diatrizoate (Hypaque) and whole blood in a ratio of 3:1. Admixture of blood was found necessary to prevent ventricular fibrillation. Two to four milliliters of these nonclotting mixtures were required for radiographic visualization of these vessels. Complete patency of the coronary arteries prior to occlusion is shown by the arteriogram in figure 2.

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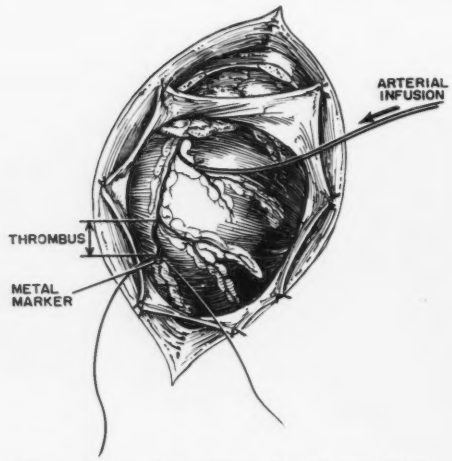

FIG. 1. Fenestration method for the production of serum-induced coronary thrombi and serial coronary arteriography. A medium-sized coronary artery is occluded by a thrombus wedged into a stenosing ligature (indicated by a radiopaque metal marker).

Coronary thrombi were produced consistently by inducing a "hypercoagulable state" in a dissected segment of a coronary artery. The distal end of this segment was narrowed by a stenosing ligature, indicated by a radiopaque metal marker, to prevent slipping of the clots to be formed. The control arteriograms revealed that these ligatures merely narrowed and did not totally occlude the artery (fig. 2). The arterial segment was isolated between 2 clamps for 10 minutes. Bulging intracoronary clots were formed within 2 minutes in this isolated segment after rapid intraluminal injection of a mixture of blood and freshly prepared serum from the operated animal in a ratio of approximately 0.5 ml. of serum to 2 ml. of freshly drawn blood. The clotting time of this mixture was tested in vitro prior to injection. Admixture of serum was found to reduce the Lee-White clotting time from 5 to 8 to 1 to 2 minutes. To produce large clots consistently, it was found necessary to prevent escape of injected material prior to clotting by clamping the finest side branches originating from the occluded segment. This modification of the method described by Wessler[7] resulted in firm thrombi with varying proportions of fibrin, platelets, and red cells. To prevent hemorrhage from the puncture site, electropolished no. 30 hypodermic needles* were used to enter the lumen.

*Stainless no. 30 hypodermic needles purchased from Vita Needle Co., Needham, Mass., were electropolished by courtesy of Dr. E. Knuth-Winterfeldt, Polytechnical Institute, Copenhagen, Denmark.

FIG. 2. Control arteriogram delineating the patent coronary arteries prior to occlusion.

After production of coronary occlusion, the animals were kept under anesthesia by injection of 30 to 65 mg. of sodium pentobarbital as needed for observation periods up to 15 hours.

During the experiment the change in clot size was determined at 1 to 2 hour intervals by measurement of the length of the filling defects in serial arteriograms. The final size and configuration of these thrombi were noted at autopsy and the hearts were then fixed in formalin for histologic examination. Tissue sections were chosen from the central and marginal zones of the infarcts and from the uninvolved wall of the left ventricle.

The clots were observed for at least 8 to 15 hours in the control group and until lysis occurred in the treated animals. The blood of the treated and the untreated animals was examined periodically to determine fibrinolytic activity by the euglobulin method and whole clot lysis time.[1]

In the treated animals an intravenous infusion of plasmin (fibrinolysin)† was started from 1 to 8 hours after production of the coronary thrombus. Infusion of 4,000 units per Kg. per hour of plasmin was sufficient to induce and maintain a fibrinolytic activity in the range of 15 to 60 minutes lysis time of a standard fibrin clot.[1] The process of clot lysis was judged by alterations in the length

†Obtained as plasmin from Merck, Sharp, and Dohme Co., West Point, Pa., and as fibrinolysin from Ortho Research Foundation, Raritan, N.J.

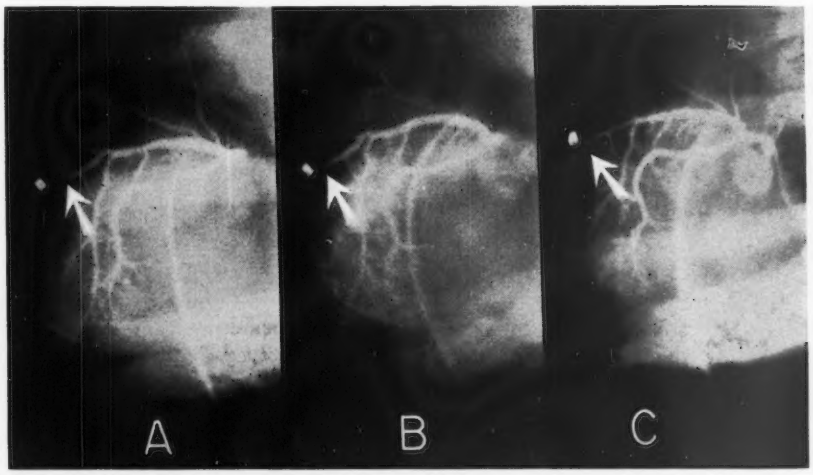

FIG. 3. Serial coronary arteriograms depicting the lysis of a coronary thrombus by systemic plasmin treatment. *A*. Arteriographic filling defect (between arrow point and metal marker) indicating size of thrombus untreated for 8 hours. *B*. Partial lysis. *C*. Complete lysis after 4½ hours of intravenous plasmin therapy. Patency of coronary arteries appears restored. The small residual filling defect is caused by the stenosing ligature.

of the arteriographic filling defects (fig. 3). The treated animals were killed within 1 hour after restoration of vascular patency in the arteriograms, the vascular tree was dissected, and the hearts were preserved for tissue studies.

RESULTS

Technical Aspects

Forty-four animals were operated upon to develop the technics for production of coronary thrombi and serial arteriography. Twenty-eight animals were lost prematurely from complications of the various procedures with termination usually in irreversible ventricular fibrillation.

Of these 28 animals 15 died prior to coronary occlusion: 5 during the dissection of coronary arteries, 5 after the first arteriogram, 2 probably from respiratory alkalosis due to overbreathing, and 3 from unknown causes. After coronary occlusion fatal ventricular fibrillation occurred in 13 animals due to excessive extent of infarction in 6, Hypaque injection in 1, hemorrhage from arterial puncture in 1, unknown causes in 3, and slipping of a coronary thrombus in 2 of the earlier experiments. Analysis of these complications and subsequent technical improvements permitted control of the predominant sources of mortality.

Arteriography as a cause of fibrillation was practically eliminated by admixture of blood to Hypaque in a ratio of 1:3 prior to intracoronary injection. This observation may be of importance in clinical angiography.

Intermittent occlusion of the coronary arteries during dissection was carefully avoided after fibrillation had been observed following sudden release of accidentally compressed vessels.

The mortality due to excessively large infarcts was greatly reduced by obstructing smaller vessels.

Effects of Plasmin

In 16 experiments coronary thrombi were produced successfully and the survival periods were sufficient for prolonged observation by serial coronary arteriography. The initial size of these thrombi and their subsequent variation in time was estimated from the length of the arteriographic filling defects. Immediately after coronary occlusion the range of clot size was 8 to 20 mm. Early retrograde extension up to the next proximal

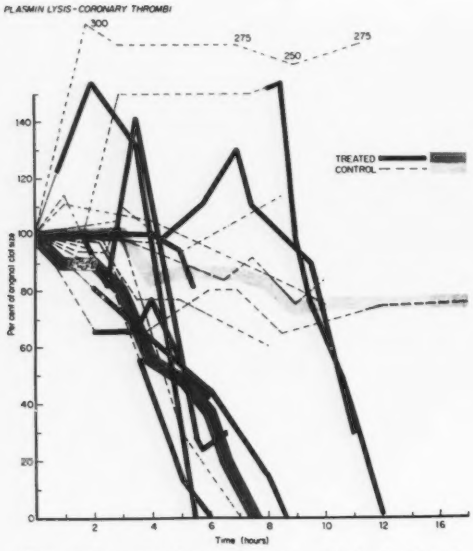

FIG. 4. Length of coronary thrombi in 8 plasmin-treated and 8 control animals. Clot size is indicated by measured length of filling defects in serial arteriograms. The curves show the relative variation of filling defects during control periods (*broken lines*) and during plasmin treatment (*solid lines*).

side branch was often observed. The alterations of coronary thrombi and the microscopic changes in early myocardial infarction will be described separately for each group.

Control Group. In 7 untreated animals coronary thrombi could be demonstrated by persistent filling defects for periods up to 15 hours (fig. 4). From 7 to 15 hours after coronary occlusion an average decrease of 20 per cent was observed in the size of the filling defects, which can be accounted for by clot retraction and possibly minimal lysis. Two of these control animals developed fatal ventricular fibrillation 2 and 9 hours after occlusion. Dissection of coronary vessels at autopsy confirmed the presence of cylindrical thrombi in all 7 animals. One additional untreated animal showed spontaneous fibrinolytic activity, which resulted in disappearance of the filling defect after 7 hours.

The control animals were autopsied 10 to 15 hours after coronary occlusion or earlier in case of fatal complications. The histologic findings consequently refer to the early changes in the infarcted myocardium. The infarcts showed marked interstitial edema, dilatation and congestion of the capillary vessels, scattered focal necrosis of muscle fibers, and marked fibrinous epicarditis with subepicardial leukocytic infiltration. Microthrombi were frequently observed. Figure 5 shows the marginal zone of a 12 hour old infarct with capillary microthrombi and vascular congestion. More severe changes were observed in the center of the same infarct with heavy edema, shrunken muscle fibers, and marked platelet aggregation in dilated vessels (fig. 6).

Plasmin-Treated Group. In the group of 8 animals treated with intravenous or intracoronary infusions of plasmin, objective evidence of lysis was obtained in all (fig. 4). Six were treated intravenously and 2 by intracoronary infusion. Fibrinolytic activity was induced 1 to 8 hours after coronary occlusion. Within 2 hours after the start of plasmin treatment progressive shortening of the filling defects became apparent. Complete lysis of coronary thrombi was achieved in 4 animals within 3 to 7 hours. Partial lysis (60 per cent or more) was observed in 4 dogs. One was killed and revealed a tiny residual clot at autopsy. Three animals succumbed to complications 3 to 5 hours after beginning of treatment (ventricular fibrillation in 1, shock due to excessive oozing from the operative wound in 1, and injection of pentobarbital in 1).

The progress of lysis of a coronary thrombus is depicted in the series of arteriograms in figure 3. The filling defects extending from the arrow point to the metal marker indicate the size of the thrombus. In this experiment total lysis of an 8 hour old thrombus was achieved after 4½ hours of systemic plasmin infused at a rate of 4,000 units per Kg. per hour.

The animals were autopsied after restoration of patency as shown by the arteriograms or earlier in the case of fatal complications. The microscopic appearance of the treated hearts was in striking contrast to the control hearts of similar duration. Treated infarcts showed less edema in the marginal areas and much less capillary dilatation and epicardial

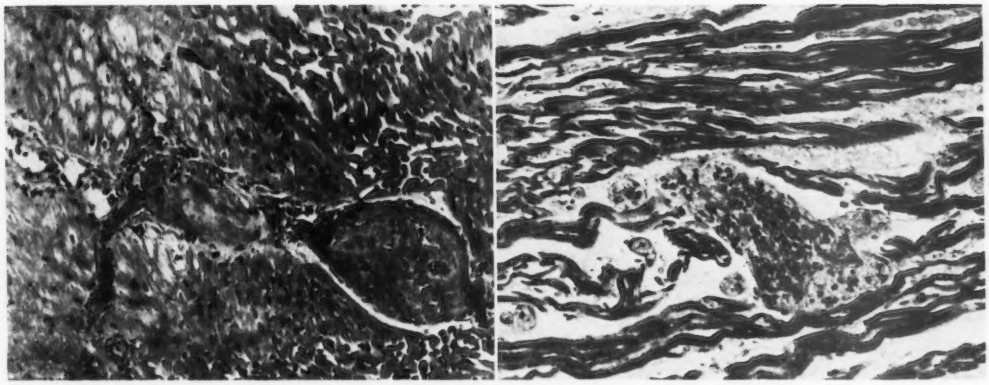

FIG. 5 *Left.* Photomicrograph of a 12 hour old untreated infarct showing the marginal zone with thrombi in capillaries and venules.

FIG. 6 *Right.* Photomicrograph showing the central zone of the infarct in figure 5 with heavy interstitial edema, shrinkage of muscle fibers, and massive platelet aggregation in a dilated vessel.

fibrin deposits in both central and marginal areas. No microthrombi could be detected in the treated group, suggesting that they may have been either prevented or dissolved. These changes occurred even without complete lysis of the primary thrombus, indicating that plasmin may penetrate the infarcts by collateral perfusion.

Figure 7 is considered representative of a 13 hour old infarct, where coronary circulation had been restored after 6 hours of plasmin treatment. Capillary thrombi and vascular congestion are completely absent. There is moderate edema and some focal muscle cell necrosis with cell invasion.

The predominant tissue changes were graded according to frequency and severity to show the contrast between the treated and the control group (fig. 8). We were unable to find any histologic evidence of damage in the animals treated with plasmin. There was no hemorrhage or evidence of increased necrosis.

DISCUSSION

These experiments prove the dissolution of intracoronary thrombi by the fibrinolytic enzyme, plasmin, within 4 to 8 hours. The composition of these thrombi approximates the constituents of clots in clinical thrombosis. The speed of lysis is the same as for experimental peripheral venous and arterial clots.[5, 6, 8, 9] In man peripheral thrombosis has been successfully treated by plasmin although the speed has not been accurately measured.[4] Since successful lysis of thrombi located at various sites of the circulatory system has been proved in animals and man, the feasibility of fibrinolytic therapy in human coronary thrombosis appears established.

The objective of fibrinolytic therapy is restoration of blood flow to organs by lysis of vascular blockade. The chances for success depend upon the tolerance of the organ to ischemia. It is well known that the time limits of viability are quite different in various organs. Earlier studies suggested that temporary coronary occlusion for more than 30 minutes would result in irreversible myocardial damage similar to permanent occlusion.[10, 11] However, more recent reports indicate that the duration of ischemia may not be the sole factor determining the time limits of viability. Myocardial anoxia may be tolerated for periods up to 2 hours during hypothermia[12] or during perfusion of the heart with heparin-containing solutions.[13]

The mechanism of ischemic injury has been studied in detail by Bing and his associates in terms of survival time of excitability, energy production, and energy utilization of

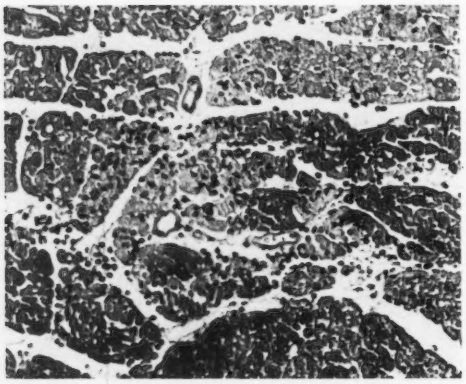

FIG. 7. Photomicrograph of a 13 hour old infarct in which coronary circulation was restored after 6 hours of plasmin treatment. The central zone is shown with moderate interstitial edema and some focal muscle cell necrosis with cell invasion. Note absence of thrombi, hemorrhage, and vascular congestion.

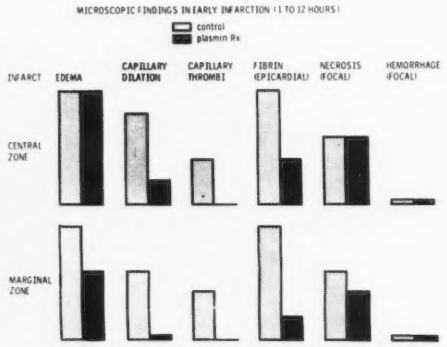

FIG. 8. Early microscopic changes in treated infarcts in comparison to controls. The predominant tissue changes up to 12 hours were graded roughly according to frequency and severity. Treated infarcts compared to controls of similar duration showed less interstitial edema in marginal zone, much less vascular congestion and epicardial fibrin deposits in central and marginal areas. Microthrombi were often seen in the control group, none were detectable in the treated hearts.

the heart muscle.[14] It was found that each of these vital functions deteriorates at a different rate that depends in all probability on the resistance of biochemical and biophysical processes to anoxia.

The experimental evidence seems to indicate that the time limit of reversible ischemic injury or myocardial viability is very flexible and related only in part to the length of ischemia. Preservation of the patency of the capillary bed by heparin and slowing of cardiac metabolism by hypothermia appear to extend the myocardial viability.

No data have been reported on the effect of the fibrinolytic state upon the ischemic myocardium. In our studies, the early stages of infarction showed a different histologic structure after induction of the fibrinolytic state. Compared to controls, the plasmin-treated infarcts showed less vascular congestion, less edema, decreased fibrinous epicarditis, and absence of capillary thrombi. These changes sometimes appeared within 1 hour of plasmin therapy, before lysis of the thrombus occluding the main coronary vessel.

These observations suggest that fibrinolytic blood may affect not only the initial occluding thrombus, but penetrate into the infarct itself by collateral perfusion. Studies are now in progress to determine whether rapid restoration of the patency of the capillary bed may influence the viability of the ischemic myocardium by improving the supply of oxygen and metabolic fuels.

Since no deleterious effects of plasmin, such as myocardial rupture or intramyocardial hemorrhage, were observed, we think that our experimental evidence offers a sound rationale for a trial of fibrinolytic therapy of human myocardial infarction. With the recent development of purified preparations of plasmin for human use, such a study is now possible.

ACKNOWLEDGMENT

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SUMMARY

Forty-four dogs were used to develop a technic for production of serum-induced coronary thrombi. The fate of these thrombi was followed by serial coronary arteriography.

In an untreated control group of 8 animals the coronary thrombus peristed in 7. In 1 animal with spontaneous fibrinolytic activity the thrombus disappeared.

Significant fibrinolytic activity was induced in 8 dogs by systemic infusions of plasmin. Total lysis of the coronary thrombus was achieved in 4 within 3 to 7 hours. Partial lysis of 60 per cent or more was observed in 4.

In comparison to controls of similar duration, the plasmin-treated infarcts showed less vascular congestion and edema and decreased fibrinous epicarditis. Also striking was the complete absence of microthrombi, which were frequently seen only in the control hearts.

SUMMARIO IN INTERLINGUA

Quaranta-quatro canes esseva usate pro disveloppar un technica de inducer thrombos coronari per medio de sero. Le destino del thrombos esseva studiate per arteriographia coronari in series.

In un grouppo de 8 animales que recipeva nulle tractamento, 7 monstrava persistentia del thrombos coronari. In le octave, spontanee activitate brinolytic resultava in le disparition del thrombo.

In un gruppo de 8 canes, grados significative de activitate fibrinolytic esseva inducite per le infusion de plasmina in le circulation systemic. Lyse total del thrombo intra 3 a 7 horas esseva effectuate in 4 de iste animales. Lyse partial de 60 pro centro o plus esseva observate in le altere 4.

In comparation con infarcimento de simile duration in animales de controlo, le infarcimento in animales tractate con plasmina esseva associate con minus sever grados de congestion vascular e de edema e con reducite grados de epicarditis fibrinose. Frappante esseva etiam le complete absentia de microthrombos in le animales tractate con plasmina. In le animales de controlo, microthrombos esseva vidite frequentemente.

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Anomalous Atrioventricular Excitation (Wolff-Parkinson-White Syndrome)

By Louis Wolff, M.D.

An opportunity to study the mechanism in pre-excitation was provided by 3 patients with unusual features: coexistence of right bundle-branch block and pre-excitation, occurrence of 2 types of anomalous ventricular complex, and simultaneous occurrence of pre-excitation and varying grades of atrioventricular block (first degree to complete). The conclusion was reached that a functioning structural atrioventricular neuromuscular bypass is present in these cases.

ALTHOUGH there is general agreement that premature depolarization of a fraction of ventricular muscle accounts for the abnormal electrocardiogram in the Wolff-Parkinson-White syndrome, there is considerable difference of opinion as to the manner in which it is brought about.[1] The problem has been investigated in many ways: study of the electric phenomena associated with the heart beat; the effect on the cardiac mechanism of various pharmacologic agents and maneuvers, including exercise and carotid sinus stimulation;[2] experimental procedures in both animals and man aimed at, or inadvertently producing, electrocardiograms resembling those occurring naturally in patients with the disorder; the anatomic demonstration of accessory atrioventricular (A-V) tracts; and the experimental creation of a short circuit between atria and ventricles capable of reproducing all the features seen in the pre-excitation syndrome. Although final proof is lacking, the weight of evidence favors the hypothesis of anomalous excitation taking place via a functioning accessory muscular bridge that bypasses the A-V node.[3]

The A-V node delays passage of the impulse as it moves from the upper to the lower chambers; when the node is bypassed the A-V transmission interval is abbreviated. A different concept has been proposed, that the shortened transmission interval is the consequence of accelerated conduction in the tissues of the A-V node.[4]

Evidence bearing on the problem will be presented in this paper consisting in vectorcardiographic observations, analysis of arrhythmias, and the demonstration of retrograde conduction from ventricles to atria via an accessory pathway.

Observations

Vectorcardiograms in 4 Patients with Wolff-Parkinson-White Syndrome

The vectorcardiograms reproduced in figures 1 to 4 were obtained from 4 patients with the Wolff-Parkinson-White syndrome.*[5] Patients exemplifying a wide range in age and cardiac status were chosen (table 1). The earliest forces, which correspond to the anomalous component or delta wave of the QRS complex, are remarkably similar in all the patients. Since these forces represent premature depolarization of ventricular myocardium, this similarity suggests an identical pathway and mechanism leading to pre-excitation.

The presence of infarction in the anterior and posterior walls of the left ventricle, and of the interventricular septum, apparently does not alter the anomalous mechanism in the cases studied (cases 2 and 4).

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*Presented at the Conference on "The Electrophysiology of the Heart" under the auspices of The New York Academy of Sciences and the U.S. Public Health Service National Heart Institute, February 16 and 17, 1956.

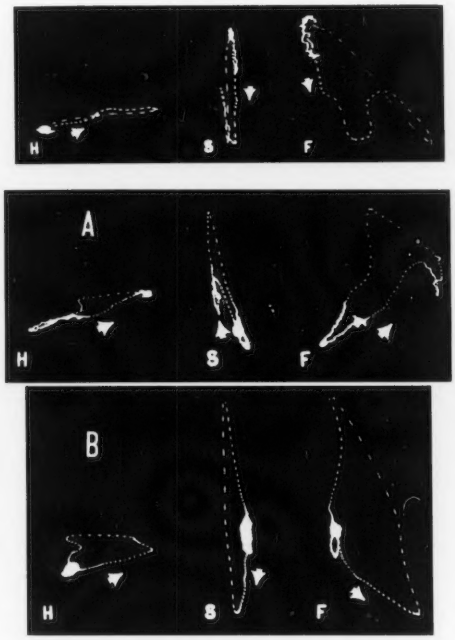

FIG. 1 *Top.* Vectorcardiogram in case 1 (5 year old girl). In figures 1 to 4 *arrows* indicate direction of inscription of the QRS loop, and each interruption equals 0.0025 second. H = horizontal, S = sagittal, and F = frontal plane projection. The *bottom* of the figure is anterior (H) or inferior (S and F), and the *top* of the figure is posterior (H) or superior (S and F), in relation to the patient. The observer's left corresponds to right (H and F), or posterior (S), and the observer's right to left (H and F), or anterior (S) in relation to the patient.

FIG. 2 *Bottom.* Vectorcardiograms in case 2 (55 year old man with anterior myocardial infarction). The infarct is concealed in the tracing with anomalous conduction (A), but is clearly evident when conduction is normal (B). Inferior infarct is simulated in the anomalous curve (A).

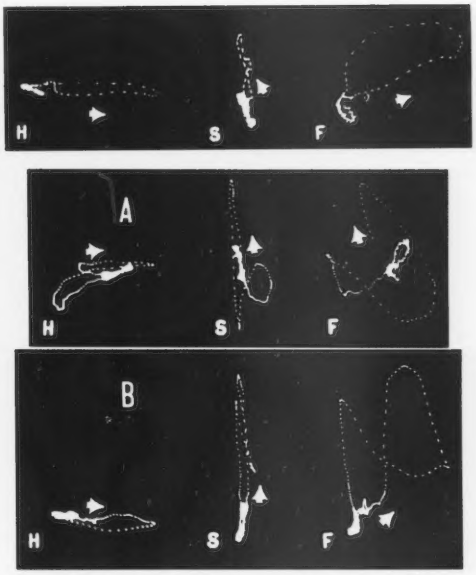

FIG. 3 *Top.* Vectorcardiogram in case 3 (58 year old man with normal heart).

FIG. 4 *Bottom.* Vectorcardiograms in case 4 (78 year old man with extensive myocardial infarction and right bundle-branch block). The infarction is concealed in the vectorcardiogram with anomalous conduction (A), but is clearly seen in the tracing with right bundle-branch block (B).

Similarly, right bundle-branch block in case 4 does not alter the *anomalous* mechanism, so that right bundle-branch is excluded as the anomalous pathway. The earliest forces in the right branch block tracing (figure 4*A*) represent ventricular depolarization via the left bundle, and those in the tracings with anomalous conduction (figure 4*B*) depolarization via the anomalous tract. Since the spatial orientation of these forces is strikingly different, the left bundle-branch may be eliminated as the anomalous pathway.

The claim has been made that disease in the A-V node is responsible for accelerated conduction in portions of the normal A-V connections.[4] However, there is little probability of A-V nodal disease in at least 2 of the 4 cases here described. Since the initial forces in the 4 cases are similar, it is probable that the anomalous pathways are identical. Therefore, if the concept of accelerated conduction is valid, one would have to postulate acquired A-V nodal lesions of a kind which would affect identical portions of the A-V conducting mechanisms; the concept envisages specific destinations of impulses starting in different parts of the A-V node.[4] Furthermore, it has been shown above that the anomalous mechanism utilizes neither the right nor the left bundle-branch; one or the other in all probability would be involved if portions of the normal

TABLE 1.—*Earliest and Terminal Forces and Clinical Diagnoses in Four Patients with the Wolff-Parkinson-White Syndrome*

Case no.	Age	Earliest forces	Terminal forces	Type (Rosenbaum[11])	Clinical diagnosis
1	5	LPD	LPU	B	? Congenital heart disease, slight cardiomegaly
2	55	LPU (LPD)*	LPU (LPU)*	B	Anterior myocardial infarction (confirmed at autopsy)
3	58	LPU (RAU)*	LPU (LPU)*	B	Normal heart
4	78	LOU (RPU)†	RAU (RAU)†	A	Anterior, posterior, and septal myocardial infarction (confirmed at autopsy); right bundle-branch block

*Normal A-V conduction.

†Right bundle-branch block.

L = left, P = posterior, D = inferior, U = superior, O = no anterior or posterior displacement.

A-V connections were used by the accelerated impulse. While it is possible on theoretical grounds that accelerated conduction might occur near an area of injury, or in areas suffering from some marginal deficiency, there is no proof of such injury and no proof that accelerated conduction actually occurs under the specified conditions.[6] Moreover, such a situation, if it existed, would probably be unstable and temporary.

The diversity and specific nature of the cases studied make it appear unlikely that an anomalous center of impulse formation is responsible for the abnormal vectorcardiogram in all of them.

Finally, all that is required to reconcile the diversity of the cases and the striking similarity of the spatial orientation of the earliest forces of depolarization is the existence of an anatomic functioning accessory pathway located in approximately the same area in all 4 cases.

Arrhythmias

The electrocardiograms reproduced in figures 5 to 7 were obtained on a 53 year old man (case 5) with the Wolff-Parkinson-White syndrome. There was no clinical evidence of heart disease other than paroxysmal tachycardia that had been present for 20 years. Paroxysms occurred with great frequency and evoked annoying palpitation. He died suddenly and unexpectedly 2 years after the tracings were recorded.

A number of short paroxysms of tachycardia were recorded during an observation period of over 2 hours, some of which are reproduced here (figures 6 and 7). Normal ventricular complexes were present in several of the paroxysms, but never in the presence of a sinoatrial mechanism. Two varieties of abnormal ventricular complex were noted when the sinus mechanism prevailed, one of them commonly, the other rarely; the common type never occurred with atrial premature beats, or during paroxysmal rapid heart action.

A complete set of leads (fig. 5) demonstrates the presence of anomalous atrioventricular excitation. A sinoatrial rhythm and the rare type of ventricular complex are displayed in figure 6, *top;* there is a single atrial premature beat which is followed by a ventricular complex of the same morphologic type. The common variety of anomalous ventricular complex is displayed in the first 3 and last 3 beats in figure 6, *middle.* The middle 3 beats constitute a short paroxysm of tachycardia initiated by a premature P wave, and the ventricular complexes are of the rare type;

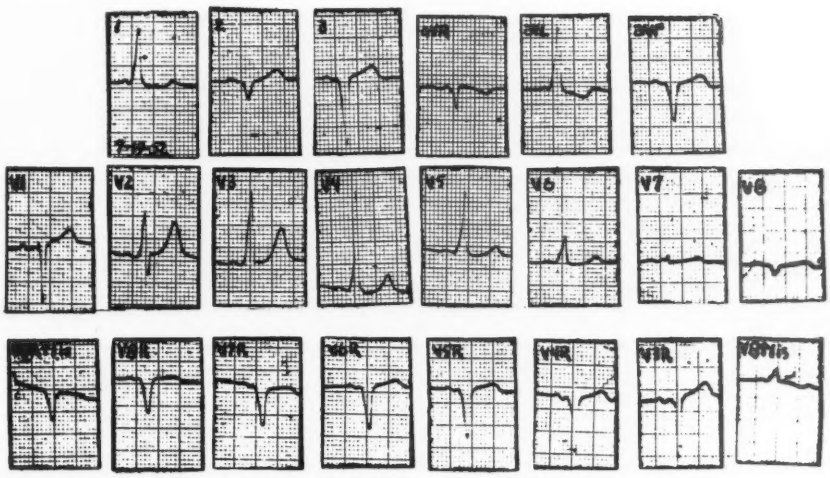

FIG. 5. Case 5. Anomalous atrioventricular excitation.

the P-R interval is abbreviated, and is even shorter than the anomalous P-R interval associated with the sinoatrial rhythm.

A longer paroxysm, again displaying the rare type of ventricular complex, is seen in figure 7, *top,* and, like the shorter one, is initiated by a premature atrial contraction. The QRS-T deflections present with the sinoatrial mechanism before and after the paroxysm are of the common variety. As in the shorter paroxysm (fig. 6, *middle*) the abbreviated P-R interval is shorter than the anomalous P-R interval during the dominance of sinoatrial rhythm. The cycle length initiating the paroxysm is the same in both; and the rate is 166 per minute in both.

A paroxysm with an identical rate, 166 per minute, but with normal ventricular complexes and normal P-R interval is shown in figure 7, *bottom.* The cycle length of the ventricular complex initiating the paroxysm is slightly longer than that of the corresponding beats in figures 6, *middle* and 7, *top* and longer than the cycle length in the remainder of the paroxysm. This is the result of the longer transmission interval through the A-V node compared to that through the anomalous pathway. The P-R interval is identical in all 3 paroxysms. Prolongation of the R-R interval does not occur in figures 6, *middle,* and 7, *top,* because the first QRS in each paroxysm represents a change from one anomalous pathway to the other with the onset of the paroxysm, rather than a shift from an anomalous pathway to the normal A-V connections. The first QRS-T complex of the paroxysm in figure 7, *bottom,* is different from both the normal and the anomalous beats, probably due to the sudden shortening of the cycle length and consequent aberrant intraventricular conduction. Both paroxysms in figure 7 are followed, after 2 sinus beats, by a ventricular premature contraction with a compensatory pause.

The ectopic atrial pacemaker responsible for the tachycardia in figures 6, *middle,* and 7, *top and middle,* is the same in all the paroxysms. In figures 6, *middle,* and 7, *top* the P-R interval is abbreviated and the QRS-T complex is anomalous, presumably because the ectopic impulse is conducted over a bypass, the one which is rarely used when the heart rate is slow, and the pacemaker is in the S-A node (fig. 6, *top*); in figure 7, *bottom,* the impulse reaches the ventricles via the normal atrioventricular connections, consequently the P-R interval and the QRS-T complex are of normal length.

Ventricular premature beats of identical contour occur in figures 6, *bottom,* and 7, *top and bottom.* The first interrupts a sinus mechanism with the rare type of ventricular complex, the last 2 a sinus mechanism with

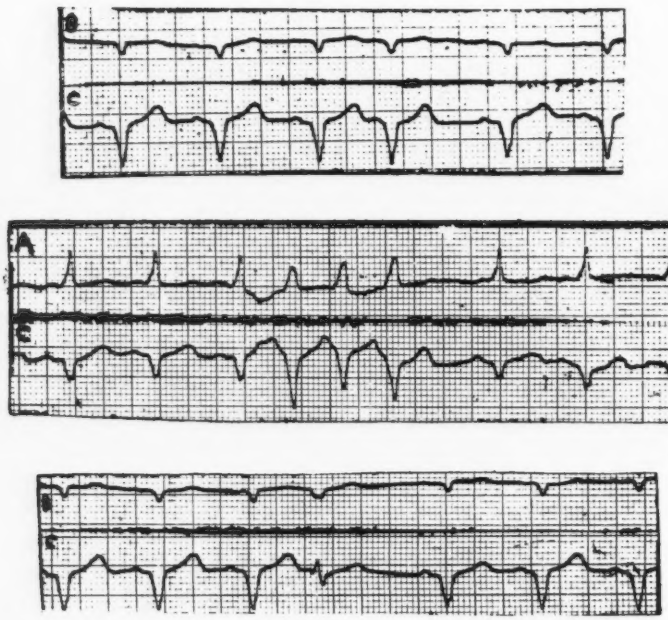

FIG. 6. Case 5. Atrial and ventricular premature beats and paroxysmal atrial tachycardia. *A, B,* and *C* are bipolar orthogonal leads in horizontal, sagittal, and vertical axes, respectively. *Top.* One atrial premature beat with anomalous excitation. Leads *B* and *C* recorded simultaneously. *Middle.* Short paroxysm of atrial tachycardia with anomalous ventricular beats differing from the sinoatrial beats. Leads *A* and *C* recorded simultaneously. *Bottom.* One ventricular premature beat with compensatory pause. Leads *B* and *C* recorded simultaneously.

the common type of ventricular complex. The coupling of the premature beats is fixed, but different from that which initiates the paroxysms of tachycardia, and the cycle length during the rapid heart action. The basic heart rate is variable, so that the fixed coupling suggests a re-entrant phenomenon. Since the course pursued by the anomalous impulse is different for each type of complex, it is unlikely that the re-entrant area lies within the anomalous pathway. The fixed coupling and morphology of the premature beats must mean that part of the sinus impulse traverses the normal A-V connections and somewhere along this pathway encounters the re-entrant area.

The cycle length of the premature beat in figure 6, *top,* differs from that of the ventricular premature beats. This beat is morphologically similar to the prevailing sinus complexes and there is no compensatory pause. These features indicate that the mechanism is different from that responsible for the ventricular premature beats. Indeed, the occurrence of an abnormal P wave and abbreviated P-R interval establishes the diagnosis of an atrial premature beat followed by the same kind of atrioventricular excitation that exists during normal sinus rhythm.

These phenomena can be explained by the existence of 2 different bypasses which act as detours for atrioventricular conduction. These pathways are separate and distinct from the A-V node. One is the preferred pathway when the heart is under sinoatrial control, the other is the exclusive anomalous pathway when atrial premature beats or paroxysmal tachycardia occurs.

The fact that there is a preferred pathway when a sinus mechanism prevails suggests that the atrial end of this pathway is more acces-

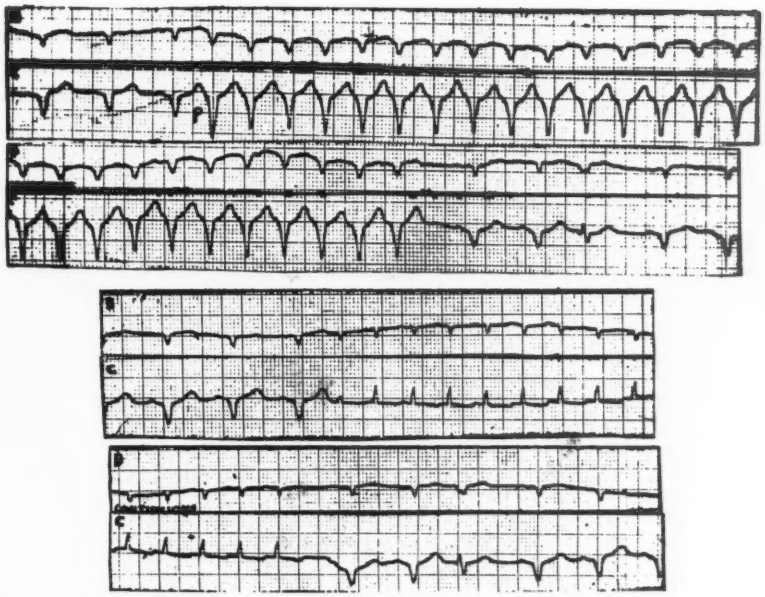

FIG. 7. Case 5. Leads *B* and *C* are bipolar orthogonal leads in sagittal and vertical axes, respectively. *Top.* Paroxysmal atrial tachycardia with anomalous ventricular complexes differing from the sinoatrial beats. One ventricular premature beat with compensatory pause. Leads *B* and *C* recorded simultaneously and mounted as continuous electrocardiogram. *Bottom.* Paroxysmal atrial tachycardia with normal ventricular complexes. One ventricular premature beat with compensatory pause. Leads *B* and *C* recorded simultaneously and mounted as continuous electrocardiogram.

sible to the sinoatrial impulse than is the origin of the alternate pathway. The latter is the exclusive anomalous pathway for atrial premature beats and paroxysmal atrial tachycardia, suggesting that its origin alone is accessible to the impulse arising in the ectopic atrial focus. The evidence supports the view that a single ectopic atrial focus is responsible for the atrial premature beats and all the paroxysms of atrial tachycardia observed.

There is no evidence of disease of the A-V node, in that signs and symptoms of heart disease are completely absent, and the A-V conduction intervals are normal. The features of the ventricular premature beats indicate that conduction through the normal A-V connections occurs simultaneously with anomalous excitation. Part of the sinus impulse which is transmitted via the A-V node to the ventricles enters the re-entrant area and is responsible for the ventricular premature beats with fixed coupling.

These data cannot be explained by anomalous impulse formation or accelerated conduction through a portion or portions of the A-V conducting system.

Retrograde Conduction

A 22 year old Negro (case 6) was hospitalized after being hit on the head by the tailboard of a truck; he was rendered unconscious for 15 minutes. His only complaints were weakness and dull left parasternal pain. The physical examination disclosed an accentuated pulmonic second sound and a faint systolic murmur in the pulmonary area, but was otherwise not remarkable. There was no cardiac enlargement by x-ray, and the white cell count, erythrocyte sedimentation rate, and Kahn tests were normal.[7]

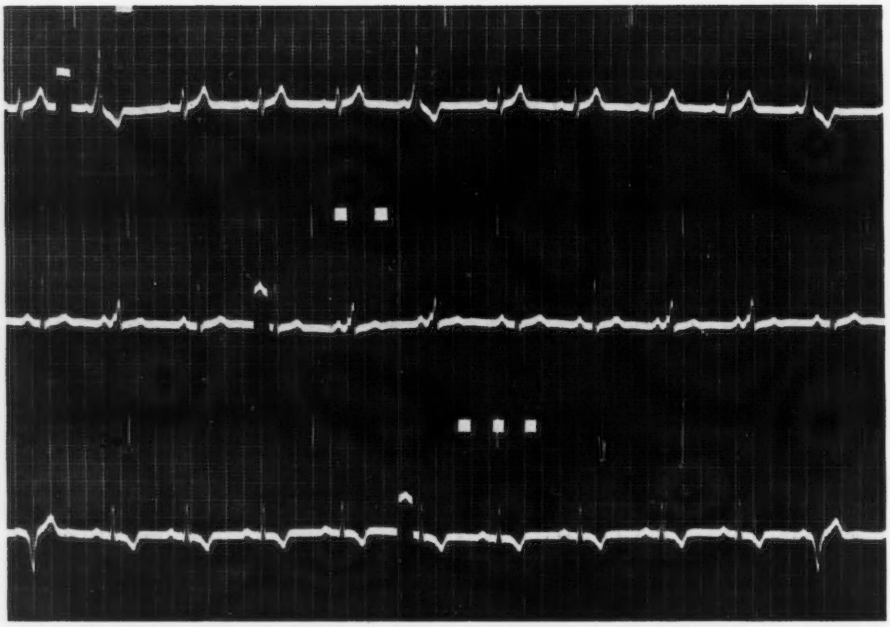

FIG. 8. Case 6. Leads I, II, and III. Intermittent anomalous atrioventricular excitation. Normal and anomalous P-R intervals constant. Note sharp upstroke of R following delta wave of anomalous beats.

The day after admission he complained of increased weakness and inability to sleep because of persistent precordial pain radiating into the left shoulder and left upper arm. Comfort was secured with codeine and an uneventful course ensued.

Electrocardiograms were obtained on August 29, August 30, September 3, and September 4, 1945.

The electrocardiogram in figure 8 reveals pre-excitation. Most of the beats are normal, but anomalous complexes occur singly, and in groups of 2 or 3. The "normal" P-R interval is constant at 0.19 second, and the anomalous P-R interval is 0.13 second; the P-J interval of the normal and anomalous complexes is 0.27 second. A sharp upward deflection follows the delta wave in the anomalous ventricular complexes in lead II.

The electrocardiogram in figure 9 discloses first degree A-V block, and normal ventricular complexes with a single exception in lead II; the rhythm is bigeminal. The P-R interval of the first beat in every pair is 0.18, and of the second beat 0.19 to 0.31 second. The P-J interval of the first beat of every pair and of the single anomalous complex in lead II, is 0.28 second. Inverted P waves (P′) are superimposed on the S-T segments of the beats which initiate the long pauses, i.e., the second beat of each pair, and the third beat of the triad. The ventricular complexes which precede the P′ deflections invariably are of the normal variety. There are 36 normal and 1 anomalous complex, and 18 inverted P waves. The RP′ intervals are constant at 0.12 second.

The electrocardiogram in figure 10 displays first degree and high grade A-V block and intermittent pre-excitation; the beats are arranged in groups separated by long pauses. In each cluster of anomalous beats there are at least 2 types of abnormal QRS-T complex. An inverted P wave invariably deforms the S-T segment of the last ventricular complex of a group, except when the latter is anomalous.

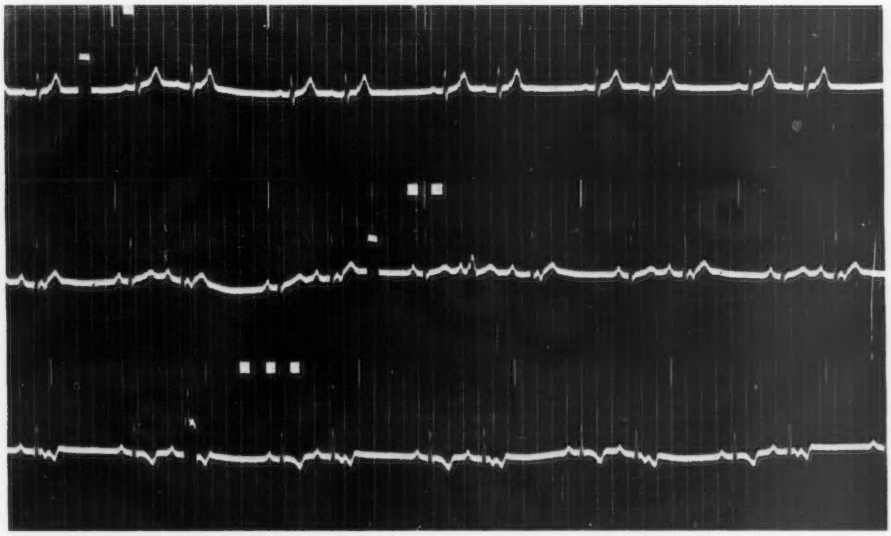

FIG. 9. Case 6. Leads I, II, and III. First degree A-V block and variation of "normal" P-R intervals. Constant R-P′ intervals.

In this circumstance all the QRS-T complexes in the group are abnormal, and the P wave which follows the last QRS-T is blocked (Wenckebach phenomenon). The anomalous P-R interval is constant, but the "normal" P-R interval varies between 0.31 and 0.39 second; the P-P intervals, at times, display progressive lengthening. The first beat in each group is anomalous. The QRS-T complex preceding the inverted P wave is normal without exception, whether or not the group contains 2, 3, or more beats. The first beat of every group displays a sharp upstroke or downstroke which is missing in the subsequent anomalous beats. The RP′ intervals are constant at 0.12 second. The entire tracing contains 12 normal and 37 anomalous beats, and 11 inverted P waves.

The electrocardiogram reproduced in figure 11 is normal; the P-R interval is constant at 0.19 second.

INTERPRETATION OF ELECTROCARDIOGRAMS

The sharply inverted P waves are characteristic of retrograde conduction, either via the A-V node, or an accessory muscular bridge connecting the lower and upper chambers. Retrograde conduction of the sinoatrial impulse by way of re-entry through the A-V node may occur when the combination of retarded antegrade conduction in one section of the node and unidirectional block in another exists; if the P-R interval is sufficiently prolonged, retrograde conduction through the area of unidirectional block will occur. The presence of retrograde P waves after normal P-R intervals (fig. 9) excludes this possibility in the case under discussion.

The other possibility, retrograde conduction through an accessory A-V pathway, is supported by the facts. Inverted P waves never follow anomalous complexes because the muscular bypass *ef*, just having transmitted the sinus impulse to the ventricles, and the activated myocardium at *f* (fig. 12) are refractory. The normal depolarization front and the anomalous depolarization wave meet and become extinguished, precluding access of the normal impulse to the accessory tract. That the association between a normal QRS-T and P′ is not fortuitous is demonstrated in figure 9; the second QRS-T of each group of beats is followed by an inverted P with a single exception, that of the anomalous beat of the triad

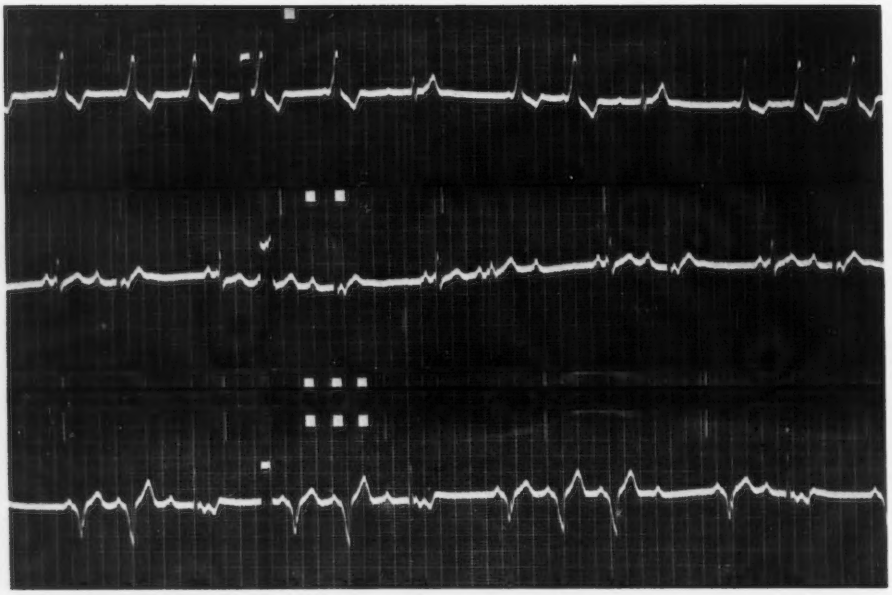

FIG. 10. Case 6. Leads I, II, and III. First degree and high grade A-V block. Variation in anomalous complexes. Wide range of "normal" P-R intervals, with constant R-P' intervals. Lengthening P-P intervals.

in lead II; the third beat of the triad, however, is normal and is followed by a retrograde P wave. The interdependence of inverted P waves and normal ventricular complexes is indicated by their respective incidence in figures 9 and 10; the lack of complete numerical correspondence between normal ventricular complexes and inverted P waves is due to the fact that retrograde conduction does not occur unless there is prolongation, no matter how slight, of the normal P-R interval (fig. 12). Inverted P waves never occur after the first QRS-T of a group of beats, either because the leading beat is anomalous, as it is, without exception, in figure 10, or because the "normal" P-R interval of the first beat of a group is not long enough, as in figure 9.

If one offshoot of the sinus impulse in the first beat of each pair in figure 9 is conducted through the A-V node, and another simultaneously penetrates the accessory A-V bridge but is not delivered to ventricular muscle, abnormal prolongation of the refractory period of the anomalous bundle must be the cause. This refractoriness prevents retrograde conduction through the accessory A-V connection when the normal depolarization front reaches the ventricular portion of the bypass *f* (fig. 12). However, minimal increase in the normal P-R interval (second beat of each pair in figure 9) allows complete recovery by the time the normal depolarization wave reaches *f*; retrograde conduction follows. The capricious and unpredictable appearance and disappearance of anomalous beats in pre-excitation may be explained by this characteristic of the accessory tract. Changes in vagal tone and in heart rate are the known factors that influence the refractory period and thereby affect conduction. The pattern of increasing P-P and P-R intervals in figure 10 is undoubtedly a manifestation of changing vagal tone. Data of a different sort, presented elsewhere,[8] led to the conclusion that vagal control plays an important part in anomalous conduction.

Retrograde conduction via a muscular bypass is consistent with the brevity and constancy of the R-P' intervals, despite the wide

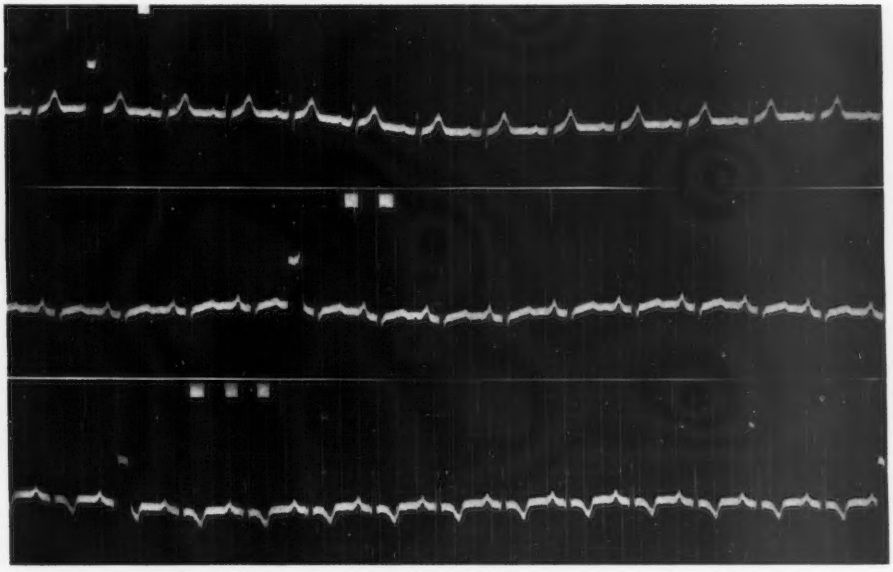

FIG. 11. Case 6. Leads I, II, and III. Normal electrocardiogram.

range of the preceding P-R intervals. It is probably more than coincidence that the anomalous P-R interval and the R-P′ interval are approximately of the same order of magnitude; the anomalous P-R interval is a measure of conduction time over pathway *aef*, while the R-P′ interval is a measure of conduction time over pathway *dgfe* (fig. 12); the anomalous tract, *ef*, with a transmission interval estimated to be 0.06 second, is common to both pathways.

The R-P′ interval is remarkably constant, and is 0.12 second regardless of the length of the preceding P-R interval. It is similar, in this respect, to the remarkable constancy of the anomalous P-R interval under widely varying conditions. Undoubtedly a single explanation is applicable to both phenomena, involving, in part, a single pathway for the impulse which is responsible for the anomalous P-R interval and for the retrograde RP′ interval; this is the tract *ef*. Since the QRS interval of the normal beats displays no variations, the transmission interval *dgf* (fig. 12) will be constant. There is no reason to suppose that variations in atrial transmission rates occur under the existing conditions; indeed, the duration of the P waves is constant throughout all the electrocardiograms. Therefore, if the tissues of the common pathway are endowed with an extremely brief relative refractory period, variations (first degree block) of the conduction interval will not occur though complete block will; this is in keeping with the facts.

The P waves are sharply inverted because the atrial end of the muscular bypass is far removed from the S-A node, lying either near the A-V node, or in the left atrium. Since the A-V node is asymmetrical in relation to the atrial mass the mean axis of atrial depolarization will be oriented to the left when retrograde conduction begins near the A-V node, and to the right when the bypass is connected to the left atrium. Consequently the P′ deflection in lead I will be upright (or diphasic) in the former and inverted in the latter situation. In the case under discussion the P′ waves in lead I are inverted, suggesting that the atrial end of the bypass is related to the left atrium.

Other mechanisms that have to be consid-

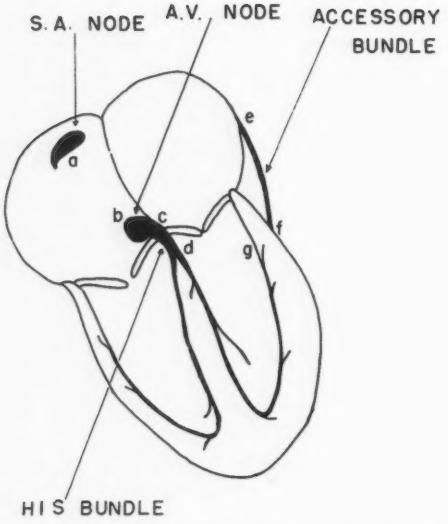

FIG. 12. Case 6. Normal A-V pathway *abcd*, and anomalous A-V pathway *aef*. The time required for the sinoatrial impulse to reach the ventricular myocardium via *abcd* is 0.18 second (fig. 9), and via *aef* is 0.13 second (fig. 8); the former is the normal P-R interval, and the latter is the anomalous P-R interval. The known facts in relation to conduction in atrial and ventricular muscle, A-V node, and Purkinje tissue permit the following transmission intervals to be postulated:[15] $ab = 0.06$, $bc = 0.11$, $cd = 0.01$, $ae = 0.07$, $cf = 0.06$, $fg = 0.04$, $abcdgf = 0.24$, and $abcdge = 0.30$ second. Interval *cd* may lie anywhere between 0.001 and 0.01 second, depending on the proportion of Purkinje fibers in this area; for our present purpose it matters little whether it is 0.01 or 0.001, so long as the same value is used in all the calculations. Interval $df = 0.06$ second, which is the interval between the beginning of QRS and the peak of R in normal complexes in lead III.

If the sinoatrial impulse uses both pathways simultaneously, and the anomalous offshoot is blocked at the ventricular end of the anomalous tract (*f*), conduction through the latter will not be evident. The normal offshoot of the sinoatrial impulse will reach the area of block via *abcdgf* in 0.24 second. It is not conducted beyond *f* when the normal P-R interval *ad* is 0.18 second, but reaches its destination in the atria when the P-R interval is 0.19 second (fig. 9). It is noteworthy that the retrograde conduction interval RP′ is constant at 0.12 second, with a range of magnitudes of the preceding P-R interval from 0.19 to 0.39 second. When the preceding P-R interval is 0.18 second retrograde conduction does not occur. Since first degree A-V block of anomalous conduction is not observed under these unique conditions, it is postulated that the relative refractory period of the accessory bundle is very brief.

ered as possible explanations for the inverted P waves are the premature discharge of ectopic atrial or A-V nodal centers and direct mechanical or electric stimulation of the atria by ventricular contraction.

The morphology of the abnormal P waves, the absence of either fixed coupling or a common cycle length, and the exclusive occurrence of P′ deflections after normal ventricular complexes militate against their origin in an ectopic atrial focus.

The constant R-P′ intervals suggest a "lower" A-V nodal mechanism with antegrade and retrograde conduction producing ventricular complexes and inverted P waves, respectively. However, the constancy of the R-P′ intervals despite the pattern of orderly and progressive increase in the P-R intervals is against this possibility. Failure of the A-V node to escape during the long pauses is also inconsistent with this explanation.

Direct mechanical or electric stimulation of the atria by ventricular contraction has been suggested as a cause of the ventriculophasic sinus arrhythmia that occurs in A-V block[9] and must be considered as an explanation of the inverted P waves in the electrocardiograms under discussion. Since the refractory period of atrial myocardium is not a factor, the apparent dependence of inverted P waves on prolongation of the P-R interval is inexplicable on the basis of direct stimulation. The latter, likewise, does not explain the occurrence of inverted P waves exclusively after normal ventricular complexes. Furthermore, it is not known that direct stimulation of the type mentioned is capable of producing sharply inverted P waves, or P waves of constant morphology, as observed here.

The most plausible explanation, then, for the inverted P waves is retrograde conduction through a muscular bypass circumventing the A-V node and functioning as a short circuit between the lower chambers and the left atrium.

DISCUSSION

Theories dealing with the mechanism of pre-excitation may be divided into 2 fundamentally different groups: an anomaly of con-

duction, and an anomaly of impulse formation. In acute experiments designed to prove the concept of anomalous impulse formation electrocardiograms have been obtained which resemble clinical pre-excitation, but it is likely that ectopic impulse formation or other definitive mechanisms differing from pre-excitation are responsible for the observed phenomena. Experimental production of perpetual anomalous impulse formation has not been achieved. On the other hand, there is available considerable evidence of different kinds in support of the hypothesis of a muscular bypass of the A-V node, and new data have been presented in this paper.

Atrioventricular conduction in the Wolff-Parkinson-White syndrome displays properties that sharply differentiate it from conduction through the A-V node. The P-R interval is markedly abbreviated in the former, and, though variations in its length are not observed, complete blockade of the pathway occurs frequently and under many conditions.[10] On the other hand fluctuations in transmission intervals over the normal A-V route are common and at times striking, but complete block is infrequent. Evidently the relative refractory period of the tissues of the accessory tract are remarkably brief in contrast to its marked prolongation, at times, in the A-V nodal tissues. In pre-excitation, quinidine and procaine amide either block A-V conduction completely or appear to have no effect on transmission intervals; they prolong conduction time without completely blocking passage of the impulse in the normal A-V bridge.[1] Digitalis is capable of prolonging or completely blocking conduction in the A-V node, while it apparently favors anomalous atrioventricular conduction without changing the transmission interval.[2] Vagal stimulation may prolong A-V conduction time or temporarily block the normal pathway, and it may dislocate the pacemaker from the S-A to the A-V node. In pre-excitation vagal stimulation does not change anomalous conduction time and has no other effect on anomalous conduction provided the cardiac pacemaker remain in the S-A node. It may cause the appearance of anomalous conduction if performed when the mechanism is normal,[11] or, as in the presence of a normal mechanism, may dislodge the pacemaker from the S-A to the A-V node, at the same time converting anomalous to normal ventricular complexes.[2]

These contrasts suggest that the tissues of the anomalous pathway and the A-V node are fundamentally different. These observations, together with others presented above, cannot be reconciled with the concept of accelerated conduction, which envisages conduction rates in the tissues of the A-V node greatly in excess of those with which we are familiar, and which treats the A-V node as the "central nervous system" of the ventricles.[4] These data provide no evidence that specific linkage of elements of the A-V node to predetermined fractions of ventricular myocardium is responsible for the anomalous complexes.

The hypothesis of a pathway that bypasses the A-V node is based on considerable experimental and clinical knowledge. The histologic demonstration of such pathways,[12] their experimental creation,[13] and a vast amount of electrocardiographic data[14] support this concept. Certain tissues, for example atrial myocardium, conduct impulses at rates far in excess of the A-V node. Such tissues by creating a short circuit, make it possible for the impulse to escape the delaying action of the A-V node. The location of the accessory tract, whether imbedded in the A-V node, or far removed from it, is important only in respect to its effect on the morphology and duration of the anomalous complex; it so happens that the evidence indicates that the bypass is usually far removed from the A-V node. If the concept of accelerated conduction in the A-V node were correct, the tissues carrying the anomalous impulse would be expected to lie within or close to the node. The observations presented above reveal no such proximity.

If it is agreed that direct stimulation of one chamber by another does not occur, the electrocardiographic data here discussed can be interpreted to mean that a muscular bridge, probably the one which is responsible for the inverted P waves, is the same pathway

that conducts the anomalous sinus impulse to the ventricles and produces the delta wave. This is deduced under the stated conditions from the fact that the anomalous P-R interval is fixed, despite the presence of variable first degree and high grade A-V block of the normal A-V bridge.

The conclusion is warranted that the mechanism responsible for the Wolff-Parkinson-White syndrome is a functioning structural accessory A-V bridge that bypasses the A-V node, where normally the impulse is delayed. Early delivery of the impulse to the lower chambers initiates premature ventricular activation with consequent shortening of the P-R interval and lengthening of the QRS interval. Retrograde conduction through the same pathway occurs, and is a possible explanation for the atrial arrhythmias that occur in the syndrome. The noteworthy observation that the anomalous P-R interval and the retrograde R-P′ interval are constant under a wide variety of conditions strongly suggests that part of these transmission intervals is a measure of conduction time through one and the same pathway.

Summary

Vectorcardiographic and electrocardiographic data in patients with the Wolff-Parkinson-White syndrome have been presented.

The significance of the spatial orientation of the earliest forces in the vectorcardiogram, an analysis of arrhythmias, and the demonstration of retrograde conduction have been applied to a study of the mechanism of anomalous atrioventricular excitation.

The data support the concept of one or more accessory functioning structural bypasses anatomically and functionally separate and distinct from the atrioventricular node.

It has been shown that the accessory tract is capable of retrograde conduction, thus providing a possible mechanism for atrial arrhythmias.

Summario in Interlingua

Es presentate datos vectocardiographic e electrocardiographic ab patientes con le syndrome de Wolff-Parkinson-White.

Le signification del orientation spatial del fortias initial in le vectocardiogramma, un analyse de arrhythmias, e le demonstration de conduction retrograde esseva applicate al studio del mechanismo de anormal excitation atrioventricular.

Le datos supporta le conception que il existe un o plure functionante shuntings structural accessori que es anatomicamente e functionalmente separate e distincte ab le nodo atrioventricular.

Es monstrate que le via accessori es capace de conduction retrograde, de maniera que illo representa un mechanismo possibile pro le arrhythmias atrial.

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John Wesley
Physician and Apothecary

"For more than twenty years I have numberless proof that regular physicians do exceedingly little good. I have, therefore, believed it my duty within the last four months to prescribe for between six and seven hundred of the poor in this city, medicine I know was proper." So began a letter written January 25, 1746, by one John Wesley, preacher, founder of the Methodist Church, scorned by the High Church of England.

John Wesley came to Oxford in June 1720, a week after his seventeenth birthday. It is not generally known that this fifteenth offspring of seventeen children spent great segments of his time in the study of medicine and natural philosophy at this university before he was ordained five years later. His friend and first biographer said; "Natural History was a field in which he walked at every opportunity to contemplate the structure of natural bodies and the instincts and habits of the animal creation." As a matter of fact, it was with difficulty that Wesley kept his devotion to physical science from trespassing upon his call to preach the gospel.

After his ordination and before he left for his mission in Georgia in October 1735 he made "anatomy and physic the diversion of his leisure hours."

In Georgia he continued to administer to the sick in body while carrying on his ministry to the spirit. He was interested in medicine as practiced by the Indians, and studied the native herbs from which they concocted their medical brews. He must have known Dr. Samuel Nunez, Spanish-speaking Portuguese Jew, first practitioner of medicine in the colony of Georgia, who had anchored at Tybee Island July 11, 1733, six months after Oglethorpe's arrival. For Wesley writes in his Journal about learning Spanish from his Jewish parishioners.

And he knew and exchanged medical lore with John Regnier, male nurse of the Moravians, and helped Regnier do the first autopsy in Georgia. The patient died because of a "Hematoma (blood clot) of the abdominal wall among other things."

After a confusing year and nine months Wesley left the New World on board the *Samuel* in December 1737 and returned to both his preaching and body healing in England—ALFRED A. WEINSTEIN. *John Wesley Physician and Apothecary.* The Georgia Review **10**: 1, 1956.

Hereditary Occurrence of the Pre-Excitation (Wolff-Parkinson-White) Syndrome with Re-Entry Mechanism and Concealed Conduction

By WILLIAM W. HARNISCHFEGER, M.D.

The hereditary occurrence of the pre-excitation (Wolff-Parkinson-White) syndrome in 3 generations of 1 family is reported. The syndrome was observed in a grandfather, father, in a set of identical twin girls, and in the male of a second set of fraternal twins. Completed abortive circus movements with re-entry into the normal conduction pathway, as well as concealed forward conduction, in the pre-excitation syndrome are demonstrated. The importance of this observation for the understanding of the mechanism of the Wolff-Parkinson-White syndrome is discussed.

AN INTERNATIONAL panel discussion on "Anomalous Atrioventricular Excitation" sponsored by the New York Academy of Sciences resulted in the advancement of 3 main concepts as an explanation for the pre-excitation syndrome.[1]

A mechanism was proposed by Sodi-Pallares, Calder, and associates that certain areas high in the interventricular septum are hypersensitive and, therefore, very easily stimulated and that the stimulus responsible for the excitation of these areas does not travel by any anatomically recognizable pathway. These authors were able to produce experimentally by right heart catheterization ventricular complexes with "remarkable likeness" to those found in clinical examples of the pre-excitation syndrome.[1, 2]

A second theory of Prinzmetal, Kennamer, and associates was that in the Wolff-Parkinson-White (W-P-W) syndrome the atrial impulse passes to the ventricles over the normal conduction system and not by way of anomalous connections, but that the normal delay in the atrioventricular (A-V) node is partially overcome, so that the impulse in part of the node passes through more rapidly than normal, a condition which they called "accelerated conduction." They also suggested that the A-V node and the intraventricular conduction system always "supply" the same portion of the ventricular myocardium and no others.[1, 3] In the experience of these authors, the W-P-W syndrome is more commonly acquired than congenital. They observed 20 patients in whom the W-P-W syndrome was thought to be acquired as a result of disease or as a functional disorder. The majority of these cases have been patients with myocardial infarction.[1]

The third concept implies the presence of 1 (or more) accessory conduction pathways bypassing the normal A-V conduction through the A-V node.[4] This theory is supported by the anatomic demonstration of anomalous muscle bundles in human hearts carefully examined at autopsy. Recent histologic evidence suggests that the bundle of Kent, which lies subepicardially, and therefore outside the annulus fibrosus, is most likely not the accessory A-V bridge responsible for the pre-excitation syndrome. Other muscular A-V connections were described by different authors, which, on the basis of recent knowledge of the embryology of the heart, will replace the bundle of Kent in the hypothesis of an accessory muscular A-V pathway as the basis for the production of the pre-excitation (W-P-W) syndrome.[5–13]

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The opinions or assertions contained herein are those of the author and are not to be construed as official or reflecting the views of the Navy Department or of the naval service at large.

Presented in part at the Third World Congress of Cardiology, September 1958, Brussels, Belgium.

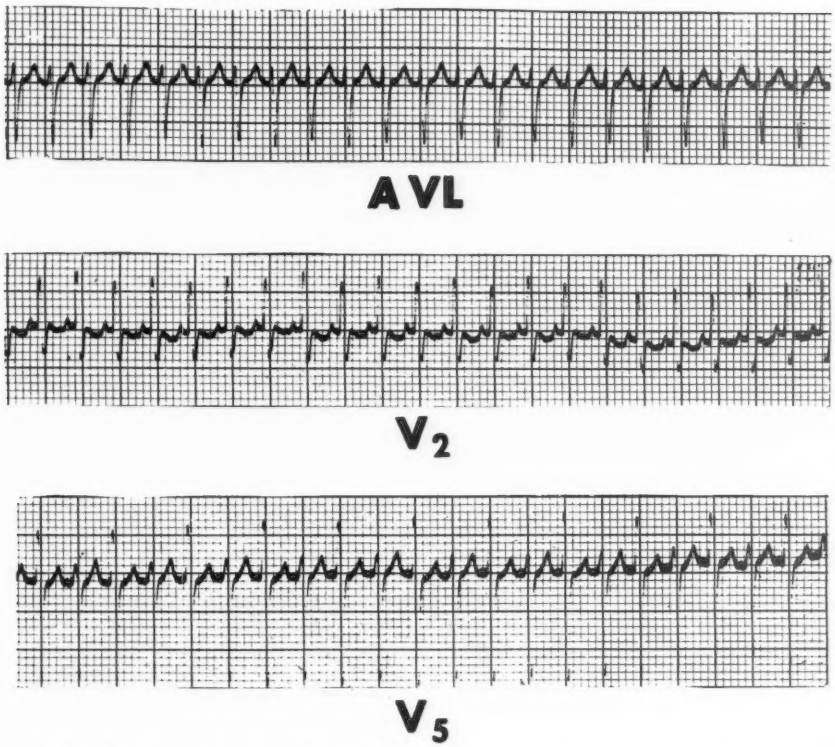


FIG. 1. Paroxysmal supraventricular tachycardia on day after admission. Note electrical alternans in V_5.

Since the original description of the syndrome,[14] voluminous monographs, excellent reviews, and many reports appeared advancing evidence in support of the different concepts. Hecht, moderator of the panel, stated in his summary and conclusion that "proof of the heredity of the syndrome would be in the observation of its occurrence in identical twins."[1]

The purpose of this report is (a) to demonstrate the occurrence of the pre-excitation (W-P-W) syndrome in 3 generations of 1 family, (b) to describe the existence of the Wolff-Parkinson-White syndrome in a set of identical twins and in the male of a second set of fraternal twins in the same family, (c) to establish evidence for completed abortive circus movements in pre-excitation—forward conduction through normal A-V pathway—return through anomalous A-V conduction path—forward re-entry through normal path, and (d) to demonstrate concealed forward conduction in the pre-excitation syndrome.

REPORT OF CASE

A 16 month old white boy was admitted to the U.S. Naval Hospital, Portsmouth, Virginia, with acute meningitis.

On the next day, an electrocardiogram showed a supraventricular tachycardia at 300 per minute, and the patient was digitalized. He was quite resistant to digitalis therapy and received over the 32 hour period a total dose of 1.05 mg. of Cedilanid (levatoside C), which is more than double his theoretical digitalizing dose.

The paroxysmal supraventricular tachycardia converted only intermittently to sinus rhythm, at times following carotid sinus pressure. An electrocardiogram in such a period revealed evidence of a pre-excitation syndrome (W-P-W syndrome). After the W-P-W syndrome was recognized as the underlying cause of the paroxysmal supraventricular tachycardia, the patient received 100 mg.

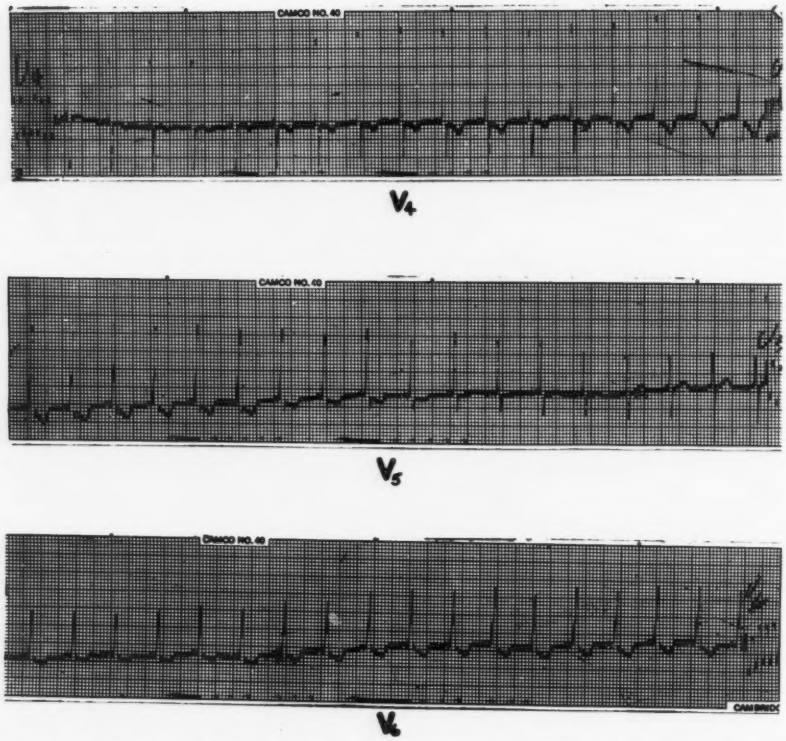


FIG. 2. Intermittent A-V dissociation produced by nonparoxysmal A-V nodal tachycardia together with pre-excitation syndrome.

of quinidine gluconate intramuscularly, and 2 hours later 200 mg. of quinidine sulfate orally. The supraventricular tachycardia was promptly controlled. The meningitis cleared with antibiotic therapy, and 5 days after admission he was afebrile, and the supraventricular tachycardia did not return. The digitoxin was discontinued after 8 days and the quinidine after 3 weeks.

The patient was discharged with the final diagnoses: meningitis, due to *Bacillus subtilis* pre-excitation syndrome (W-P-W syndrome); paroxysmal supraventricular tachycardia.

This patient was found to be of particular interest from several points of view, since he presented cardiac arrhythmias, which are readily interpreted by assuming an accessory A-V conduction bypass.

Figure 1 shows part of the electrocardiogram obtained 1 day after admission. Supraventricular paroxysmal tachycardia was diagnosed on the basis of the normal duration of QRS and the precise regularity of the rapid rhythm at the rate of 300 per minute. No P waves can be made out with certainty, although the upright peak before the QRS in V_2 probably represents a P wave. The possibility exists, but is remote, that this may be paroxysmal atrial flutter with 1:1 A-V conduction, because the rate is so rapid. Electrical alternans is especially well demonstrated during this rapid rhythm in lead V_5.

Figure 2, after digitalization with more than double the usual digitalizing dose, shows the pre-excitation syndrome diagnosed by the combination of a short P-R (0.06 second), a delta wave, and widened QRS to 0.10 second. In V_5 the W-P-W complexes change progressively in contour from left to right. The delta wave disappears and the small S wave becomes larger until the last complex in V_5 presents a diphasic R-S. In addition, the depressed S-T in the first few complexes becomes less depressed from left to right and the inverted T wave becomes less inverted and is finally upright in the last 3 complexes of V_5. The sinus rhythm shows a slight arrhythmia and varies between a rate of 120 and 130 per minute. In this tracing, we are dealing with intermittent A-V dissociation produced by nonparoxysmal A-V nodal tachycardia.[15] The A-V node escapes readily as

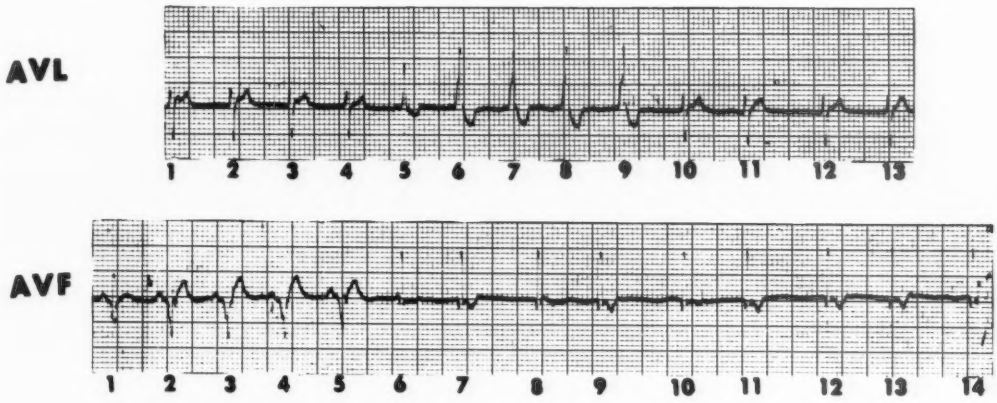


FIG. 3 *Top.* Pre-excitation (W-P-W) syndrome with intermittent A-V dissociation produced by A-V nodal tachycardia. In addition, there is concealed forward conduction and concealed re-entry of retrograde impulses into the normal A-V path present producing pseudobigeminy.

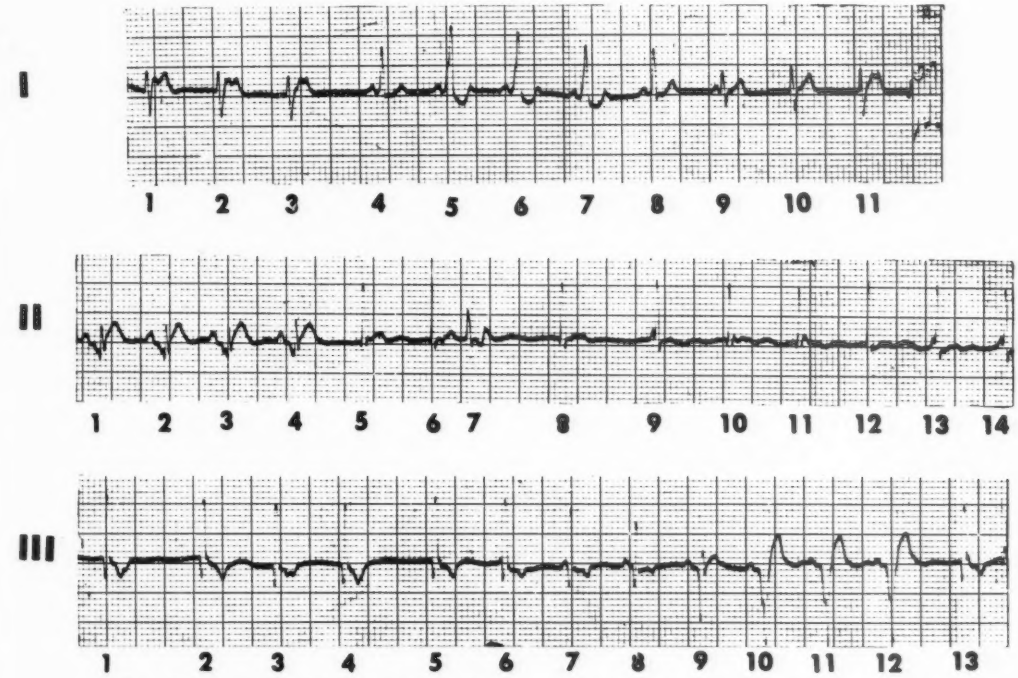


FIG. 4 *Bottom.* Concealed forward conduction and re-entry into the normal A-V pathway of a retrograde impulse following a ventricular capture.

soon as the sinus node slows down. This mechanism, which was repeated throughout the record, is of particular interest in this case of pre-excitation syndrome because of the coincidence of a sinus arrhythmia with A-V nodal tachycardia. The A-V nodal acceleration may find its cause in the infection or may be due to the high dose of digitalis.

Figure 3 represents part of long leads aV_L and aV_F. Evidence of the pre-excitation syndrome is

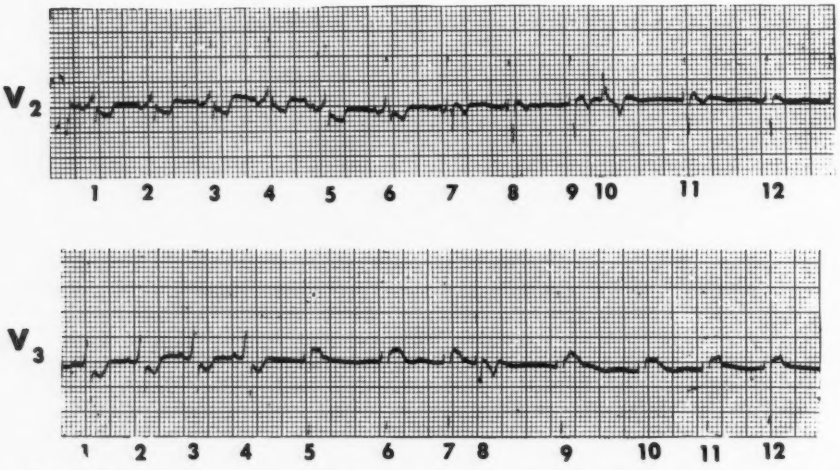


FIG. 5. Intermittent A-V dissociation due to A-V nodal tachycardia and pre-excitation (W-P-W) syndrome. Two completed ventricular captures with aberrant ventricular conduction are seen in V_2 (beat 10) and V_3 (beat 8). From the ventricular capture the impulse is conducted in a retrograde fashion to the atrium and leads to concealed re-entry into the normal A-V pathway.

based in aV_F on the combination of a short P-R (0.08 second), a delta wave, and widened QRS of 0.08 second in beats 2 to 4. The sinus rate is 136 per minute. Compared with these pre-excitation beats, complexes of entirely different contour and direction are present (beats 6 to 14): no P wave precedes the QRS complexes in these beats; they are A-V nodal escape beats producing A-V dissociation. The P wave of the fifth beat is a trifle late, and close observation of the QRS reveals a different contour from the others as evidenced by the absent delta wave and the small downward deflection before the T wave. The slight slowing of the sinus impulse by 0.04 second was enough to permit A-V nodal escape, producing A-V dissociation and electric interference at the A-V junction. The same interpretation can be applied to the first beat of this strip. On examination of the A-V nodal beats, further interesting phenomena are observed. The T waves of the beats 6, 8, and 10 are not so deeply inverted as those of the 7, 9, and 11. In addition, the inverted T waves are followed by pauses producing pseudobigeminy. On detailed analysis of the S-T segment and T-wave contour of the seventh beat in comparison with the ninth beat, it will be seen that an upright P wave is superimposed on the ST of the seventh beat and an inverted P wave is superimposed on the T wave of the ninth beat. Furthermore, on exact measurement it will be seen that the pause following the ninth beat is 0.04 second longer than the pause following the seventh. The interpretation of these pauses is that after the seventh beat the impulse formation of the A-V node is retarded by the sinus impulse traversing deeper into the A-V junction producing forward concealed conduction.[16] The pause following the ninth beat is produced by a different conduction pathway. The conduction of this A-V nodal beat spreads through the ventricle and in a retrograde fashion through an acessory A-V bridge into the atria, re-entering the normal A-V junction. The re-entry of the retrograde impulse is "concealed" in that it is not followed by another ventricular beat, but its effect on the A-V node is manifested by delay of the A-V nodal impulse formation.[16] In support of this interpretation are (a) the inverted P wave superimposed on the T wave, indicating retrograde excitation of the atria, and (b) prolongation of the pause following an inverted P wave by 0.04 second as compared with the pause following an upright P wave. The difference of 0.04 second represents the re-entry time. The same abortive circus movement of conduction is seen in beats 11, 12, and 13. However, the second last cycle of the tracing is not prolonged, despite a retrograde P wave, indicating intermittent failure of re-entry to occur. In aV_L, concealed forward conduction is clearly evident in beat 11, where an upright P wave is seen superimposed on the T wave of that beat and is followed by a pause indicative of retarded impulse formation of the A-V node.[16] In summary, in this tracing the pre-excitation syndrome

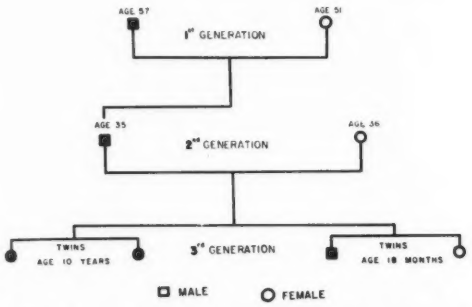


FIG. 6. Pedigree demonstrating the pre-excitation (W-P-W) syndrome in 3 generations of the Hall family. The twin girls, 10 years of age, are identical twins.

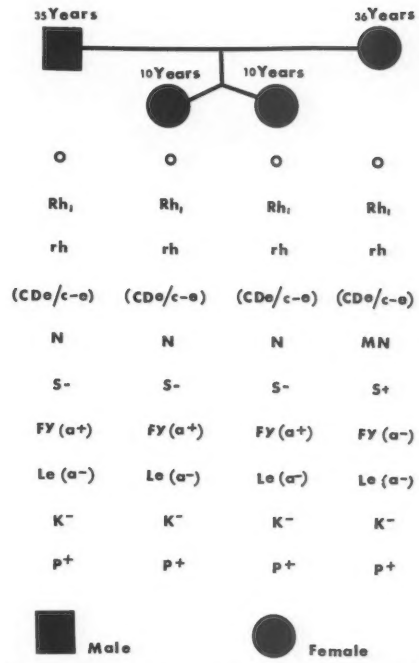


FIG. 7. The blood groups of the identical twins with pre-excitation syndrome compared with the ones of their parents. The blood groups differ from their mother's and are like the ones of their father, who also presented the W-P-W syndrome.

is the basic mechanism plus A-V nodal tachycardia which produces A-V dissociation and electric interference at the A-V junction. In addition, there is concealed forward conduction and concealed re-entry of retrograde impulses through an accessory A-V bypass producing pseudobigeminy.

Figure 4 is assembled from selected parts of long limb leads of the same patient. This tracing is especially interesting for 3 reasons: fusion beats of unusual type in pre-excitation, concealed conduction in forward direction, and concealed retrograde conduction over an anomalous accessory A-V bypass following a ventricular capture. Again the main diagnosis is pre-excitation and intermittent A-V dissociation due to nonparoxysmal nodal tachycardia. In lead I, 2 basically different QRS complexes are seen. Beats 5 and 6 represent pre-excitation complexes. The first 3 beats as well as the last 2 beats represent A-V nodal beats with electric interference at the A-V junction as evidenced by the P wave superimposed on the T wave. Beats 4, 7, 8, and 9 vary in contour and to different degrees are intermediate between the 2 basic QRS complexes: these are fusion beats. The mechanism of these fusion beats can be understood by the assumption of an accessory A-V bypass. In pre-excitation, a single impulse originates in the sinoatrial node and splits in the atrium on its way to the ventricle to use the normal conduction path as well as an accessory A-V bridge, thus producing interference in the ventricles. In this tracing, a second ectopic focus in the A-V node has to be postulated, which promptly escapes as soon as the sinoatrial node slows. Here the fusion beats are the result of admixture of these 2 foci, the sinoatrial impulse plus the ectopic one.

In lead III, intermittent A-V dissociation as basic mechanism can again be recognized. An A-V nodal arrhythmia varying between the rate of 125 and 136 is present. On 2 occasions, after beats 1 and 4, a pause is seen, the cause of which can be interpreted as concealed re-entry of the retrograde impulse to the A-V node retarding its impulse formation as described in figure 3.

The bizarre premature beat in lead II (beat 7) represents a completed ventricular capture with aberrant spread in the ventricle and retrograde conduction through an accessory A-V bypath producing concealed re-entry of the retrograde impulse. Proof for this interpretation will be supported with figure 5, where in leads V_2 and V_3 the same phenomenon occurred.

In figure 5 we again see in the first 4 beats of V_2 and V_3 evidence of the pre-excitation syndrome diagnosed on the criteria outlined previously. In V_2 the sinoatrial rhythm slows from the fifth to the seventh beat, whereupon the A-V node escapes, producing intermittent A-V dissociation with electric interference at the A-V junction. The explanation of the 2 premature complexes with detailed analysis of their mechanism is important for the understanding of the pre-excitation syndrome. Assuming the presence of an accessory A-V bypass, these 2 beats can be interpreted as follows:

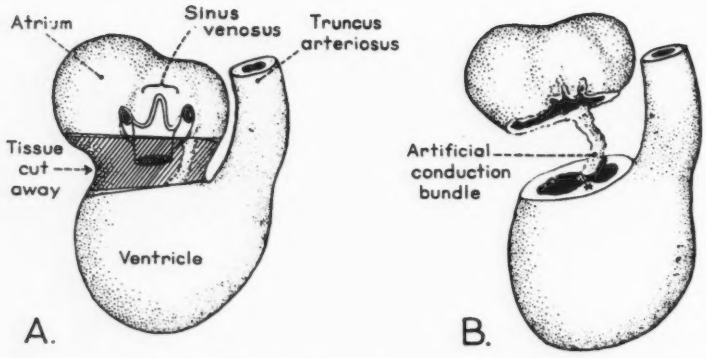


FIG. 8. Heart of a 4 day chick cut to leave a connecting muscle strand between atrium and ventricle simulating an ectopic bundle of His. *A.* Dorsal view of removed heart with diagonal hatching indicating the tissue to be cut away. *B.* Same heart after the excision had been completed. Note that the artificial bundle was made by leaving a strand of muscle in the ventral part of the heart wall, in a region as far as possible from that in which the His bundle later appears. The asterisk on the cut surface indicates the region where the His bundle would have been differentiated at a considerably later period of development. (*From Bradley M. Patten, Univ. Michigan M. Bull.* 22: *1, 1956*)

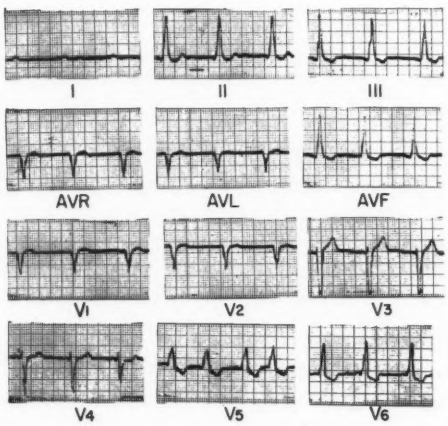
In V_2 as in V_3 the basic mechanism is intermittent A-V dissociation. On examination of the A-V nodal beats in V_2 it can be seen that the P-R distance becomes progressively shorter from left to right until in beat 9, preceding the bizarre complex, the sinus P wave appears after the QRS. Evidence for this is seen by the different contour of the S-T segment as compared with the 2 previous A-V nodal complexes. The premature bizarre beat 10 is a completed ventricular capture with marked aberrant ventricular conduction. The same interpretation can be applied for the bizarre complex 8 in V_3. With this established, the second challenge in this record is the explanation for the delayed impulse formation of the A-V node. Assuming an accessory A-V bypass, it can be postulated that the conduction of the ventricular capture is spreading backwards through the accessory A-V bridge, activating the atrium in a retrograde fashion, reentering the normal A-V path, and retarding the impulse formation of the A-V nodal focus by concealed re-entry of the retrograde impulse.[16] In support of this assumption is the fact that the duration of the R-R interval following the ventricular capture of 0.66 second is exactly the same R-R interval as in lead aV_F (fig. 3) where concealed re-entry of a retrograde impulse was established. Further, the negative deflection following the aberrantly conducted ventricular capture is a superimposed inverted P wave. Finally, the R-R interval is 0.04 second longer, representing the re-entry time, as compared with the R-R interval where forward concealed conduction was present. This tracing is unique and represents convincing evidence of the property of retrograde conductivity postulated for an accessory A-V bridge as an explanation for the mechanism of supraventricular paroxysmal tachycardia in the pre-excitation syndrome.

This represents the only demonstration in the literature for a completed abortive circus movement with re-entry into the normal A-V conduction pathway in the pre-excitation syndrome.

The possibility that the pre-excitation syndrome was a hereditary anomaly was suspected more and more in recent years since observations increased that the syndrome was found in 2 brothers[17] and parent and child.[11, 18-23] Wolff observed 5 cases in a single family.[1]

Curiosity led me to the examination of the entire family after the diagnosis of the W-P-W syndrome was established in the baby twin. The pre-excitation syndrome was observed in 2 identical female twins, sisters of the patient, and it was traced back into the third generation of the same family. Figure 6 demonstrates the pre-excitation syndrome in a grandfather, father, identical set of female twins, and in the male of a second set of fraternal twins. Documentation of the individual electrocardiograms is furnished in figures 9 to 13.

The 35 year old father of the twins was totally unaware of the presence of the W-P-W syndrome. During his career in the U.S. Navy he passed several physical examinations, but an electrocardiogram was never taken. There was no history of paroxysmal supraventricular tachycardia. The history was similarly negative in the 10 year old identical twin girls. However, 1 of the twin girls



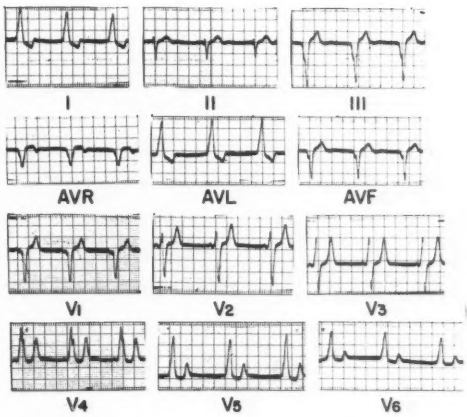


FIG. 9 *Left.* The electrocardiogram of R. C. H., a 57 year old man with W-P-W syndrome and chronic pulmonary emphysema.

FIG. 10 *Right.* Pre-excitation (W-P-W) syndrome in a 35 year old man (J. H.), son of R. C. H., asymptomatic and without clinical evidence of heart disease.

presented a systolic murmur of grade II, which was best audible along the left sternal border in the second and third intercostal space, with a slightly accentuated pulmonic sound. The chest x-ray was negative. Her electrocardiogram differed from the one of her twin sister, as can be seen in the illustrative appendix, but both are type A according to the classification of Rosenbaum and co-workers.[1, 24] The murmur was classified as insignificant for the dynamics of the heart.

The grandfather of the twins, 57 years of age, suffered shortness of breath and occasional palpitation of short duration for 5 to 7 years. He was not known to have pre-excitation syndrome. Pulmonary function studies revealed marked pulmonary emphysema.

Since the monozygotic identity of the 10 year old female twins is of prime importance for the hereditary occurrence of the pre-excitation, further support for this fact was established by examination of their blood groups. Twins with dissimilar blood groups or of different sexes are obviously dizygotic.[25] Of all twin pairs, 65 per cent are found to be like-sexed and 35 per cent unlike-sexed. If 35 per cent are unlike-sexed and dizygotic, the same percentage will be expected to be like-sexed and dizygotic. The remaining 30 per cent will be like-sexed and monozygotic pairs. Figure 7 demonstrates the blood groups of the like-sexed twins and the ones of their parents. As can be seen, the blood groups of the twins are the same and, furthermore, are like the blood groups of their father, who also presented the W-P-W syndrome. The blood groups differ from the ones of their mother in the MN, S, and Fy (a–) groups. It can therefore be concluded that the like-sexed twins are, with a high degree of certainty, really identical monozygotic twins.

DISCUSSION

A discussion of the observations described above in relation to the concept of the mecha-

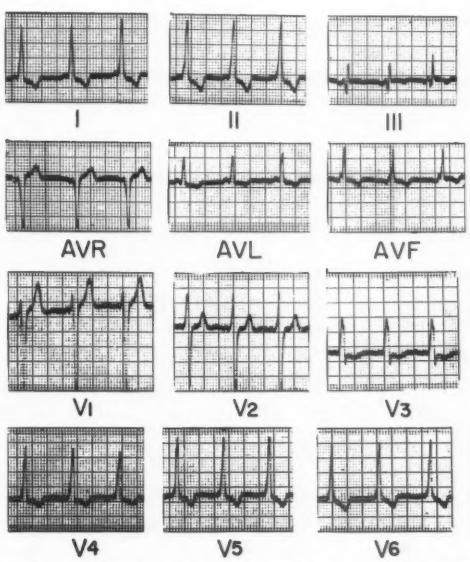


FIG. 11. Electrocardiogram of 10 year old twin M. H., daughter of J. H., demonstrating the W-P-W syndrome.

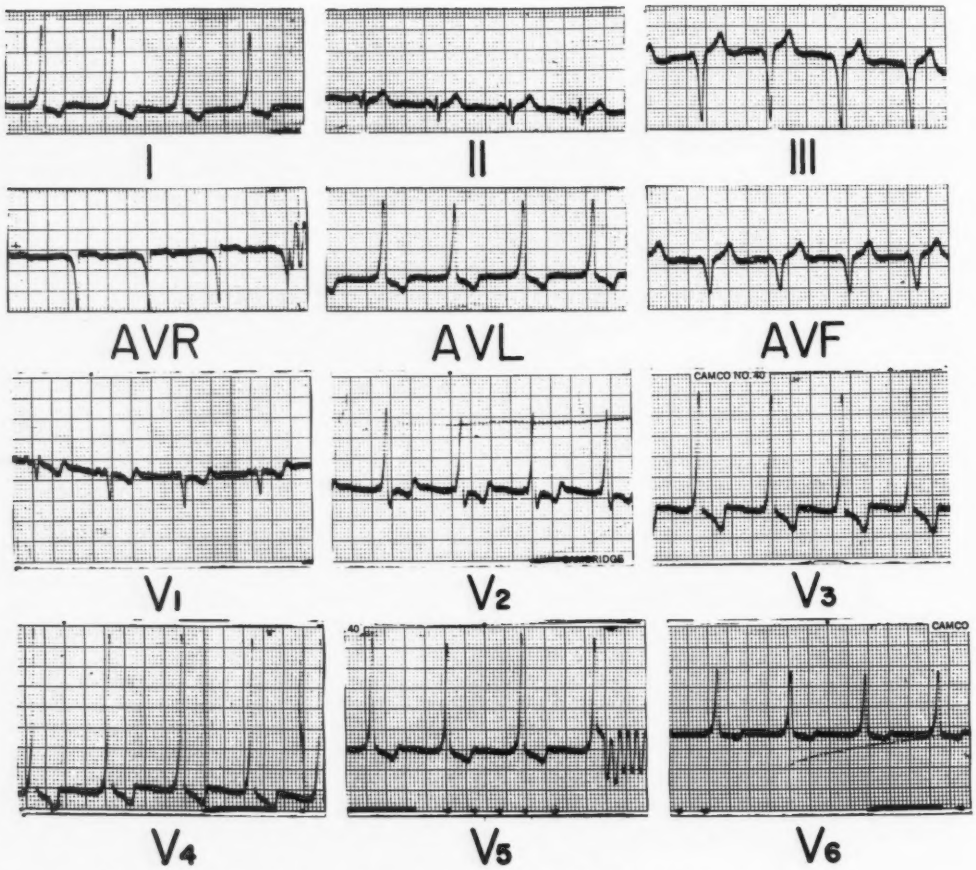


FIG. 12. Electrocardiogram of identical twin sister, M. H., with pre-excitation syndrome.

nism of the pre-excitation (W-P-W) syndrome is of interest in relation to the advances made in embryology. In support of an accessory A-V pathway is not only the anatomic demonstration of muscular A-V connections, but experiments in embryology which established further evidence that these muscular A-V connections are actually able to conduct the sinoatrial impulse to the ventricle. Elegant and very instructive experiments performed by Patten,[26] as shown in figure 8, present convincing evidence of the conductive capacity of embryonic cardiac muscle. The sinoatrial impulse to the ventricle is still conducted in spite of cutting away all the tissue around the atrioventricular constriction except for a narrow connecting strand, which then serves functionally as a sort of artificial bundle of His. Patten found that it does not make any difference whether this connecting strand is left at or near the place where the bundle of His will later develop or whether, as in figure 8, the strand is left on the opposite wall of the heart at the farthest possible distance from the normal site of the bundle of His. The utilization of a strand of muscle from a part of the heart that never becomes involved in the formation of the bundle of His avoids any questions that might arise as to the possible functional differentiation of a conduction bundle, before it is histologically differentiated. Thus, it seems only natural that certain re-

tained tracts of it come to serve as the path of impulse conduction and, on rare occasions, of impulse formation in the adult heart.

There seems to be general agreement on several points. 1. The W-P-W complex is the result of a ventricular fusion beat, the QRS complex is the resultant of 2 different conducted stimuli in the ventricle.[1, 4, 20, 23, 27-32] 2. A limited area of 1 ventricle contracts prematurely; the remaining ventricular myocardium is excited by way of the normal A-V pathway. The prematurely contracted ventricular area is already in diastolic relaxation while the remaining ventricular myocardium is still contracted.[1, 33-35] 3. In tracings designated as type A (positive delta wave in all precordial leads), the premature contraction occurs in the left ventricle and in type B (negative delta wave in right precordial leads) the pre-excitation occurs in the right ventricle.[1, 24, 33]

There are considerable divergent explanations, however, for the production of the "fusion beat" in anomalous atrioventricular excitation.[1, 2, 3, 23, 36, 37] In assuming an accessory muscular A-V bridge, the physiologic properties of conductivity and rhythmicity of such muscle fibers are essential prerequisites. That the property of rhythmicity can exist, although rarely, in the accessory A-V connection was convincingly proved by Pick and Katz.[23] The property of conductivity of such fibers both in a forward and in a retrograde direction is, however, the primary factor responsible for the usual manifestations of the syndrome. The mechanism for the forward conduction in the W-P-W syndrome was already described. Thus, as the final link in the chain of evidence for an accessory A-V conduction path it remained necessary to demonstrate conduction in a retrograde direction from the ventricle back to the atrium via the anomalous path. Proof of such evidence is given in figures 3, 4, and 5 of this report. The demonstration of a completed circus movement of conduction in a human heart is of particular importance for the understanding of the mechanism of supraventricular tachycardia in the presence of pre-excitation.

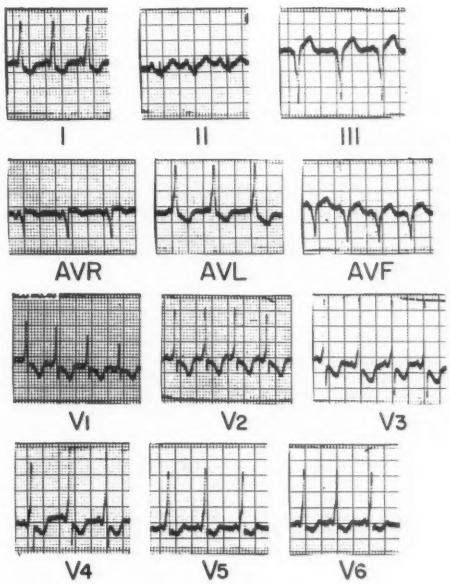


FIG. 13. Pre-excitation (W-P-W) syndrome in 16 month old baby, the reported patient, son of J. H.

As demonstrated in figures 4 and 5, impulses conducted in a normal fashion through the A-V junction to the ventricles may return back toward the atria over the accessory A-V path and continuation of such a re-entry mechanism may initiate and perpetuate rapid heart action. Further evidence for the correctness of this view is the demonstration that in cases in which the onset of supraventricular tachycardia was recorded, the last beat preceding the tachycardia was not of the pre-excitation type.[20, 23]

The recent report of Pick and Fisch[31] on 3 cases of the W-P-W syndrome in the presence of bundle-branch block is another important contribution to the existence of an accessory muscular A-V bypath. They reported left bundle-branch block and the pre-excitation syndrome in 2 cases, and right bundle-branch block and the W-P-W syndrome in 1. Thus, it is possible to explain in a rational way and on the basis of physiologically acceptable principles, the production of the ventricular "fusion beat" as well as all varieties of arrhythmias in the pre-excitation syndrome, by assuming the existence of

an accessory muscular A-V bridge. In addition, with the first demonstration of the hereditary nature of the W-P-W syndrome over 3 generations and in a set of identical twins, together with the cardiac arrhythmias reported, strong evidence is established for the correctness of the hypothesis of an accessory A-V connection as the most appropriate one to account for all of the known aspects of the pre-excitation syndrome.

Summary

The possibility that the pre-excitation syndrome can be a hereditary anomaly, as suspected in recent years, is further supported by this observation of its occurrence in 3 generations of 1 family. Convincing evidence for this is the existence of the Wolff-Parkinson-White syndrome in a set of identical twins and a set of fraternal twins in the same family. The monozygotic identity of the twins was proved by their blood groups.

The concept of the mechanism of supraventricular tachycardia in pre-excitation syndrome by impulses returning back to the atria over an accessory atrioventricular path, and continuation of such a re-entry mechanism perpetuating the rapid heart action, was strongly supported by the demonstration of completed circus movements of conduction in a human heart. The operation of a completed retrograde re-entry mechanism—forward conduction through a normal atrioventricular pathway, return through an anomalous atrioventricular conduction path, retrograde excitation of the atria, forward re-entry into the normal atrioventricular path—was demonstrated for the first time.

Atrioventricular dissociation in the Wolff-Parkinson-White syndrome with effect of concealed forward and concealed retrograde conduction upon impulse formation of the atrioventricular node is demonstrated, and the importance of this observation for the understanding of the mechanism of the pre-excitation (Wolff-Parkinson-White) syndrome is discussed.

Acknowledgment

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Summario in Interlingua

Le possibilitate que le syndrome de pre-excitation pote occurrer como anomalia hereditari—como on lo ha suspicite in recente annos—es supportate additionalmente per le hic reportate observation de su occurrentia in 3 generationes del mesme familia. Un forte corroboration es le presentia del syndrome de Wolff-Parkinson-White in un par de geminos identic e un par de geminos fraterne in le mesme familia. Le identitate monozygotic del geminos esseva demonstrate per lor gruppos de sanguine.

Le conception que le mechanismo del tachycardia supraventricular in le syndrome de pre-excitation depende del retorno de impulsos al atrios per un via atrio-ventricular accessori e que le continuation de iste mechanismo de re-entrata perpetua le rapide action del corde, iste conception esseva fortemente supportate per le demonstration de complete circos de conduction in un corde human. Esseva effectuate le prime demonstration del curso del mechanismo de un complete re-entrata retrograde, i.e. le conduction in avante per un normal via atrio-ventricular, retorno per un via anormal de conduction atrio-ventricular, excitation retrograde del atrios, e re-entrata in avante in le normal via atrio-ventricular.

Dissociation atrio-ventricular in syndrome de Wolff-Parkinson-White, con le effecto del celate conduction in avante e del celate conduction retrograde super le formation del impulso del nodo atrio-ventricular, es demonstrate. Le importantia de iste observation pro le comprension del mechanismo del syndrome de pre-excitation (syndrome de Wolff-Parkinson-White) es discutite.

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Diagnosis.—One must be a professional Ulysses in craft and wisdom not sometimes to err in estimating the nature of an attack of severe heart pain. There is no group of cases so calculated to keep one in a condition of wholesome humility. When you jostle against a hale, vigorous specimen of humanity, who claps you on the back and says, "The deuce take you doctors! I have scarcely yet got over my fright," you would like to forget that five years before you had almost signed his death warrant in a very positive diagnosis of angina pectoris vera. On the other hand, Mr. X. has left you with the full assurance that his cardiac pains are due to overwork or tobacco, and you have comforted his wife and lifted a weight of sorrow from both by your most favorable prognosis. With what sort of appetite can you eat your breakfast when, a week later, you read in the morning paper the announcement of his sudden death in the railway station? Or take another aspect—poor Mrs. Doe has gone softly all these years in the bitterness of her soul since you took that grave view of her vaso-motor or hysterical angina!—WILLIAM OSLER, M.D. *Lectures on Angina Pectoris and Allied States,* 1897.

Ballistocardiogram in Chronic Severe Anemia

By L. M. Sanghvi, M.R.C.P. (London), D.T.M. & H. (England), and K. Banerjee, M.D.

Serial ballistocardiograms of 30 patients with chronic severe anemia were studied to assess the cardiovascular state in anemia and after the cure of anemia. The findings in the ballistocardiogram have been compared to those in the electrocardiogram and the roentgenogram. Significance of an abnormal ballistocardiogram after the cure of anemia is stressed.

CARDIOVASCULAR disturbances and electrocardiographic abnormalities in chronic anemia have been extensively reported. The ballistocardiogram in chronic anemia has been reported to show large systolic complexes, minimal respiratory variation, a usually normal wave pattern but transient abnormal patterns when the hemoglobin is rapidly raised, abnormal patterns after relief of anemia in some older subjects known to have heart trouble, increased height of H, L, and N waves, and broad J waves in the presence of congestive heart failure.[1-3] There has, however, been no large-scale study. Although the great majority of the alterations are nonspecific in character, ballistocardiography is believed to be a useful physiologic means of eliciting information about the force of cardiac contraction and ejection of blood in the vessels.[4, 5] It was thought that it might be of particular value in anemia, where there is no valvular, coronary, or other type of heart disease. The purpose of this paper is to report a study of serial ballistocardiograms on 30 patients with chronic severe anemia.

Material and Methods

Thirty patients with chronic anemia and hemoglobin levels of less than 7 Gm./100 ml., and with no other cardiovascular disease, were selected for this study. All of them were hospitalized until the anemia was cured. There were 20 males and 10 females; their ages (table 1) ranged from 12 to 50 years, with an average of 27 years. The hemoglobin level ranged from 2 to 6.5 Gm. per cent, with an average of 3.3 Gm. Cardiac enlargement was present in 22 cases; the cardiothoracic ratio ranged from 51 to 89 per cent, with an average of 61 per cent. Congestive heart failure was present in 7 cases, of whom 4 were females. The anemia was caused by chronic malaria in 13 cases, ankylostomiasis in 10, uterine bleeding in 2, bleeding hemorrhoids in 2, chronic dysentery in 1, and was of undetermined etiology in 2 cases.

A 2 coil electromagnetic ballistocardiograph of the Dock type with a 20 mfd. condenser in circuit and attached in series with limb lead II of a direct recording Burdick electrocardiograph was used. The sensitivity of the recorder was standardized so that 1 mv. produced a 1 cm. deflection. Some normal ballistocardiograms with this equipment are shown in figure 1 for comparison. Patients were studied in a basal state. Tracings were recorded after 15 minutes rest in the recumbent position, during normal respiration, deep inspiration, and deep expiration. An electrocardiogram, with standard leads I, II, and III, and unipolar leads aV_R, aV_L, aV_F, and V_1 to V_6, was recorded; blood pressure and hemoglobin levels were determined at the same time. Observations were made every 2 weeks until the anemia was cured, with a further follow-up period of 4 weeks to 18 months. The average period for cure of anemia was 48 days, the average period of observation, 90 days. The criteria of Dock and associates[1] were employed to grade the ballistocardiograms. Grade 1 with a normal wave pattern was not considered abnormal. The study has been restricted to the qualitative aspect of the wave pattern. Chest roentgenograms were taken on admission and after cure of anemia. The heart was considered enlarged if the cardiothoracic ratio was more than 50 per cent or if it showed reduction in size after treatment.

Results

An abnormal ballistocardiogram was recorded in 28 cases, in 19 on admission and in 9 others after improvement of anemia. The ballistocardiogram remained abnormal in 25

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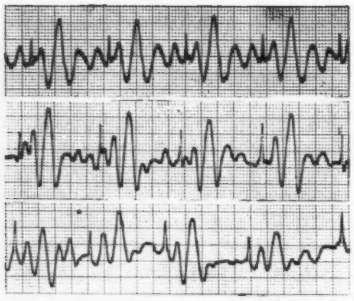

FIG. 1. Ballistocardiograms of 3 normal persons.

cases, despite cure of anemia. Ballistocardiographic findings, on admission, during the period of observation, and after cure of anemia, are given in table 2.

The abnormalities consisted of tall or bifid H; plateau-type I valley; slurred, or notched I-J and J-K segments; broad or bifid J; fused H-J; short, absent, or notched K; tall H, L, or N; and totally bizarre complexes of low amplitude. The abnormalities, their appearance after improvement of anemia, their further course, and the persistence of abnormal records despite cure of anemia are illustrated in figures 2 to 5. Large systolic complexes were seen at the time of admission in 11 cases, 5 of which had an abnormal pattern. In significant contrast to these, totally bizarre complexes of small amplitude and grade 4 abnormality were seen in 5 cases, in 4 at the time of admission and in 1 after cure of anemia. In 3 of them, records with very low amplitude and in 1, grade 4 abnormality persisted despite cure of anemia.

Of the 7 cases with heart failure 1 showed a normal ballistocardiogram on admission, which became abnormal later. Three cases showed large systolic complexes with abnormal patterns. Three of the 4 cases with tall N had heart failure, and tall H was seen in all 7 cases, though the former in each instance and the latter in 5 appeared after improvement of anemia.

Both cases with normal tracings throughout the period of observation had normal-size hearts. After the cure of anemia, 14 of the 15 cases with persistent cardiac enlargement showed abnormal ballistocardiograms and 12 had abnormal electrocardiograms, while in 15 cases with normal-size hearts the corresponding figures were 11 and 3 respectively.

TABLE 1.—*Age and Sex Distribution*

Age (yrs.)	M	F
11—20	7	2
21—30	4	4
31—40	5	4
41—50	4	—
Total	20	10

At the time of admission the ballistocardiogram was abnormal in 19 cases, the electrocardiogram in 26 cases, and one or both in 28 cases; the corresponding figures after cure of anemia were 25, 15, and 26 respectively. One case with a pattern of left ventricular hypertrophy showed a normal ballistocardiogram at all times. Instances were noted where the ballistocardiogram showed severe abnormalities at the time of admission while the electrocardiogram was normal (fig. 6).

DISCUSSION

In chronic anemia, decreased vascular resistance is likely to mask myocardial weakness, and abnormal patterns may thus be concealed even in the presence of severe myocardial damage. Again ejection by the left ventricle is facilitated by low aortic resistance with increased contribution of the left ventricle to I-J. The large impacts from the left ventricle decreasing on inspiration cancel the increase in the small impacts of the right ventricle and the respiratory variation may be minimal.[1] We were therefore impressed by the high incidence of abnormal ballistocardiograms in this series, which is no doubt due to the intensity and the chronicity of the anemia in the cases included in this study. Abnormal patterns in the ballistocardiograms were concealed at the time of admission in only one third of the cases and were seen even when the systolic complexes were large. Many of the abnormalities, some of them transient, appeared after improvement of anemia. In cases of severe anemia where the heart itself

TABLE 2.—*Incidence of Abnormal Ballistocardiograms*

	No. with abnormal BCG	Grade abnormality				Abnormality of waves					
		1	2	3	4	H	J	K	L	I-J	J-K
On admission	19	7	1	0	4	2	1	5	2	4	11
Total incidence	28	10	4	1	5	17	12	15	12	10	26
After cure	25	10	2	0	1	16	6	9	6	4	20

is injured by anoxia, the appearance of transient abnormalities when the hemoglobin is rapidly raised has been ascribed to myocardial recovery lagging behind vasoconstriction and increased resistance to ejection. Abnormal patterns have also been noted to appear after relief of anemia in some older subjects known to have heart trouble.[1] In our cases, however, abnormal patterns appeared even though the rise in hemoglobin was, as a rule, gradual and irrespective of the age of the patient. The presence of abnormal patterns at the height of anemia and of abnormal respiratory variation in nearly two thirds of our cases was significant and can only be considered to indicate such severe myocardial damage that the left ventricle is unable to accelerate the blood in a normal manner, despite the low peripheral resistance.

No specific pattern in the ballistocardiogram in anemia was revealed in this study. Tall H, notched J, slurred or notched J-K, and short K were the most frequent abnormalities. Tall H has been reported in heart failure, coronary disease, mitral stenosis, and acute myocarditis. The 2 cases that showed tall H on admission had heart failure. In 5 cases with heart failure and in 10 others, however, tall H appeared after relief of heart failure or improvement of anemia, and in 16 cases it persisted despite cure of anemia. In some of these cases tall H was considered as relative to the small I-J. But in others it seems that, because of myocardial damage, upward motion of the blood in the atria during isometric contraction was increased and produced the tall H.

The K wave in the ballistocardiogram is due to deceleration of blood in the aorta and its impact on small peripheral vessels.[6] De-

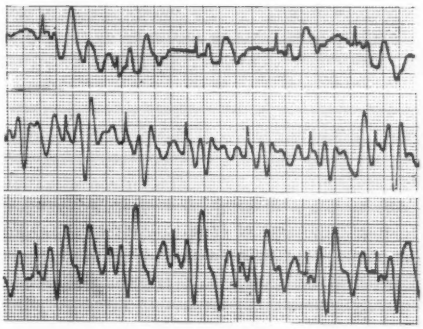

FIG. 2. Abnormal wave patterns in 3 cases. *Top*, grade I abnormality, broad I valley, and slurred J-K. *Middle*, grade I abnormality, tall H and L, notched or bifid J, and slurred J-K. *Bottom*, large amplitude of systolic complexes with slurring or notching of J-K.

creased peripheral resistance and low cardiac output diminish its amplitude.[7] Short or absent K waves have been reported in coaretation of the aorta, aortic stenosis, occlusion of the aorta, some cases of congenital heart disease, and hypotension. The occurrence of a significantly short K wave in many of our cases was noteworthy, particularly since the records were obtained with the electromagnetic instrument with which the K wave is deeper than with other types of instruments[8] and is stated to be the most prominent and deepest negative component.[9] This has also been our experience in control tracings in normal subjects. In several instances in this series the K wave was even absent or cut off and often very much delayed owing to slurring of the J-K segment particularly in expiration, a pattern which has been stated to be quite specific for coaretation or other obstructive lesions of the aorta.[10] A short K has been noted in association with vertical hearts[10] but in our cases determination of the position of the heart from the roentgenogram and the electrocardiogram showed nearly an equal incidence in cases with horizontal and vertical hearts. The short K wave in those of our cases in which it was seen on admission can be attributed to decreased peripheral resistance. In others, however, in which it appeared after improvement or persisted despite cure of ane-

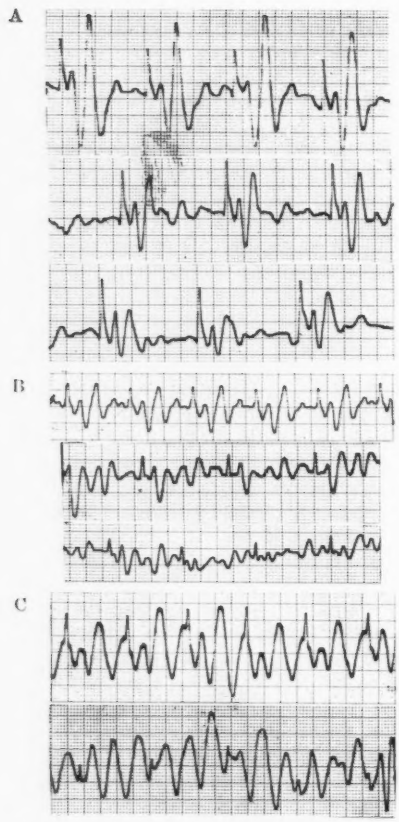

FIG. 3. Appearance of abnormal patterns after improvement of anemia in 3 cases (A, B, C) with normal pattern and with abnormally large, small, and normal amplitude of systolic complexes, respectively, on admission (first ballistogram). *A*, after cure of anemia short K waves; and 5 weeks later, tall H and slurred or notched J-K. *B*, after cure of anemia, grade 1 abnormality, and tall H, L, and N and short K waves; 5 weeks later, grade 2 abnormality with small complexes and broad, notched J waves. *C*, after cure of anemia, tall H and L waves.

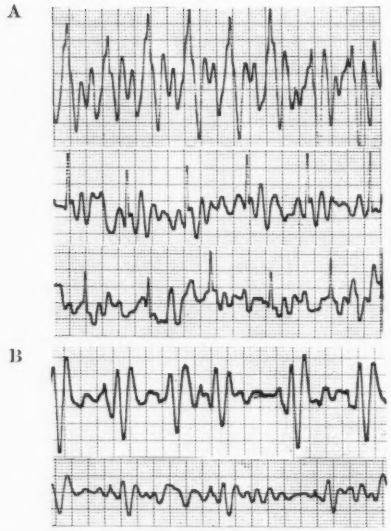

FIG. 4. Abnormal wave pattern in the presence of large systolic complexes on admission in 2 cases with heart failure; abnormal records after cure of anemia. *A*, on admission, tall H, fused H-J, and tall L; after cure of anemia, decreased amplitude, tall H, notched J and slurred J-K; 2 months later, bizzare complexes. *B*, on admission, grade 1 abnormality, tall H, slurred J-K, and short K; 6 weeks after cure of anemia, tall H, notched J, short K, and variation of H-K time from 0.28 to 0.34 second.

mia, it appears that decreased force of myocardial contraction was responsible for it.

It has been stated[1] that so far no one has shown that anything but heart failure or scars due to coronary artery disease can cause grade 3 or 4 changes or the fused H-J and notched J pattern. It was therefore of great interest to find these changes in some of our cases. Of particular interest was the presence of grade 4 abnormality at the time of admission in 4 cases of which only 1 had heart failure, and in 1 after cure of anemia. The former 4 were females with ages of 25, 30, 30, and 39 years, and the latter was a boy of 14 years. There was therefore little possibility of coincident coronary artery disease. The boy has been admitted 3 times in 2 years, each time with recurrence of heart failure due to hookworm reinfestation and recurrence of anemia, thus demonstrating the prognostic value of the ballistocardiogram at this young age.

The incidence of abnormal electrocardiograms was greater on admission. After cure of anemia, however, the incidence of abnormal ballistocardiograms was greater and while only 1 case with cardiac enlargement and 1 with an abnormal electrocardiogram (L.V.H. pattern) showed a normal ballistocardiogram, 11 cases with a normal electrocardiogram and

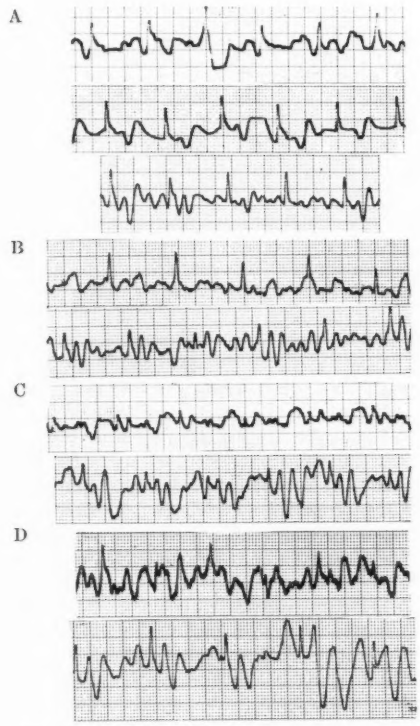

FIG. 5. Totally bizzare complexes on admission in 4 cases; abnormal records after cure of anemia. *A*, after cure of anemia, small but identifiable complexes; 8 weeks later, small amplitude, grade 1 abnormality, notched or bifid J, and slurred J-K. *B*, 9 weeks after cure of anemia, relatively tall H, and J and J-K abnormalities. *C*, 5 weeks after cure of anemia, grade 1 abnormality with tall H and L waves. *D*, 14 weeks after cure of anemia, tall H, short K, and slurred J-K.

the same number without cardiac enlargement showed an abnormal ballistocardiogram. This showed the superiority of the ballistocardiograph over these 2 conventional means of detecting residual myocardial damage. That a normal ballistocardiogram, however, does not exclude myocardial disease was seen in a case with a pattern of left ventricular hypertrophy in the electrocardiogram. Apparently the cardiac ejection may be normal in the presence of compensatory hypertrophy.

It has been suggested that significance should be attached to abnormal ballistocardiograms in subjects below the age of 50 years,[9]

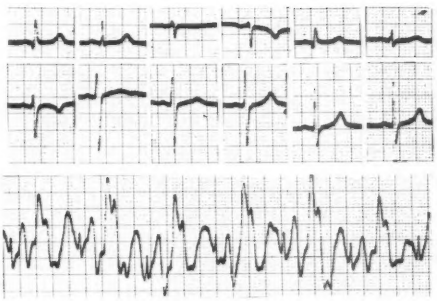

FIG. 6. Severe ballistocardiographic abnormality in the presence of normal electrocardiogram on admission.

Persistence of abnormal ballistocardiograms, even several months after cure of anemia, in many of our cases all of whom were below this age, would therefore indicate persistence of impaired mechanical efficiency of the heart, which may be permanent. With passage of time the ballistocardiogram may yet become normal in some of these cases.

It is concluded that chronic severe anemia often leads to such a severe myocardial damage that abnormal ballistocardiograms, including maximum abnormality, may be recorded despite decreased peripheral resistance, and that some damage often persists despite cure of anemia. It is stressed that in the interpreting of an abnormal ballistocardiogram in an otherwise normal individual and in the attributing of it to a possible coronary artery disease, a previous history of anemia must be excluded, particularly in countries where such anemias are not uncommon.

SUMMARY

Results of a study of serial ballistocardiograms in 30 cases of chronic severe anemia are reported. An electromagnetic ballistocardiograph of the Dock type was used.

Many of the abnormal patterns appeared after improvement of anemia. An abnormal pattern was seen in 28 cases and persisted in 25, despite cure of anemia. Maximum grade 4 abnormality was seen in 5 cases, in 4 at the time of admission and in 1 after cure of anemia. Slurred or notched J-K, tall H, and short K were the most frequent abnormalities.

No specific pattern of anemia was revealed in the ballistocardiogram.

The electrocardiogram was abnormal in 26 cases on admission and in 15 after cure of anemia. The ballistocardiogram was abnormal in 19 cases on admission and in 25 after cure of anemia.

The results of this study show that there is usually severe impairment of the functional state of the circulatory system in chronic severe anemia, that some impairment often persists despite cure of anemia, and that ballistocardiography is a valuable adjunct in its determination.

Summario in Interlingua

Es reportate le resultatos del studio de ballistocardiogrammas serial in 30 casos de sever anemia chronic. Esseva utilisate un ballistocardiographo electromagnetic del typo Dock.

Multes del configurationes anormal appareva post le melioration del anemia. Configurationes anormal esseva observate in 28 casos. In 25 illos persisteva in despecto del curation del anemia. Anormalitate del grado 4 (maximal) esseva trovate in 5 casos: in 4 al tempore del admission al hospital e in 1 post le curation del anemia. Le plus frequente anormalitates esseva J-K vage o indentate, H alte, e K curte. Un configuration specificamente anemic non esseva constatate in le ballistocardiogrammas.

Le electrocardiogramma esseva anormal al tempore del admission in 26 casos. In 15, illo esseva anormal post le curation del anemia. Le ballistocardiogramma esseva anormal al tempore del admission in 19 casos. In 25, illo esseva anormal post le cura del anemia.

Le resultatos del presente studio indica que in sever anemia chronic il ha usualmente un compromisso sever del stato functional del systema circulatori, que un certe grado del compromisso persiste frequentemente in despecto de curation del anemia, e que le ballistocardiographia es de valor como adjuncto in su determination.

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Suprasternal Transaortic Coronary Arteriography

By William M. Lemmon, M.D., J. Stauffer Lehman, M.D., and Randal A. Boyer, M.D.

Opacification of the coronary arteries has been accomplished by direct needle puncture of the ascending portion of the thoracic aorta via a suprasternal approach and injection of highly-concentrated radiopaque medium. Experience with 35 attempts in 31 patients at such coronary opacification is described. The electrocardiographic observations, the reactions, and the complications incident to the study are discussed. Thirteen of the 31 patients had some type of intrapericardial cardiac surgery subsequent to this procedure, and the surgical observations regarding the status of the coronary arteries are compared with the coronary arteriographic findings.

THE DEVELOPMENT of a satisfactory method of radiologic visualization of the coronary arteries in man has become of increasing importance with the advent of direct surgical approach to disease of these vessels.[1, 2] Previous efforts to opacify the coronary arteries in man include angiocardiography, catheter aortography, cardiac ventriculography, and direct transthoracic needle puncture of the aorta.

Angiocardiography only occasionally demonstrates the coronary arteries, basically because the injected opaque medium is too greatly diluted by the time it reaches the ascending aorta. The opaque medium in the cardiac chambers in considerable measure also obscures the coronary vessels.[3]

Injection of opaque medium through a catheter introduced into the ascending aorta by way of a carotid, radial, or brachial artery, to effect entry of the opaque material into the coronary arterial system, has produced opacification of the coronary arterial vessels.[4–6] Catheter aortography necessitates a cut-down exposure of the vessel through which the catheter is passed and thus introduces possible undesirable sequelae incident to repair of the vessel opening.

Cardiac ventriculography can effect opacification of the coronary arteries, as reported by Lehman, Musser, and Lykens.[7] Since in left-sided cardiac ventriculography the opaque medium is injected directly into the left ventricle, the left ventricular opacification obscures to a certain extent visualization of the coronary arterial supply.

In 1945 Radner[8] reported rather unsuccessful attempts at coronary opacification by direct needle puncture of the aorta through the sternum. Hoyos and Del Campo,[9] in 1948, reported opacification of the coronary arteries by a left parasternal needle puncture of the ascending aorta. Wickbom,[10] in 1952, introduced a technic of "thoracic aortography after direct puncture of the aorta from the jugulum," but he did not mention coronary artery opacification, except in his report of 1 fatality resulting from his procedure.[11]

The suprasternal approach to direct puncture of the left atrium and of the ascending aorta to obtain left atrial and aortic pressure recordings, as reported by Radner,[12] suggested to us the possibility of coronary artery opacification by injecting a highly concentrated radiopaque medium through a needle introduced into the ascending aorta via a suprasternal approach, and advancing the needle until its tip was near the coronary ostia.

Our experience with 35 attempts at suprasternal transaortic coronary arteriography in 31 patients forms the basis of this communication.

Methods and Materials

In our procedure we have adopted, in large measure, the materials and methods utilized for cardiac ventriculography.[7] We use a 17 gage, thin wall, 7 inch beveled needle, with a single side hole opening adjacent to its tip. This needle is connected by plastic tubing through a 3 way stop-

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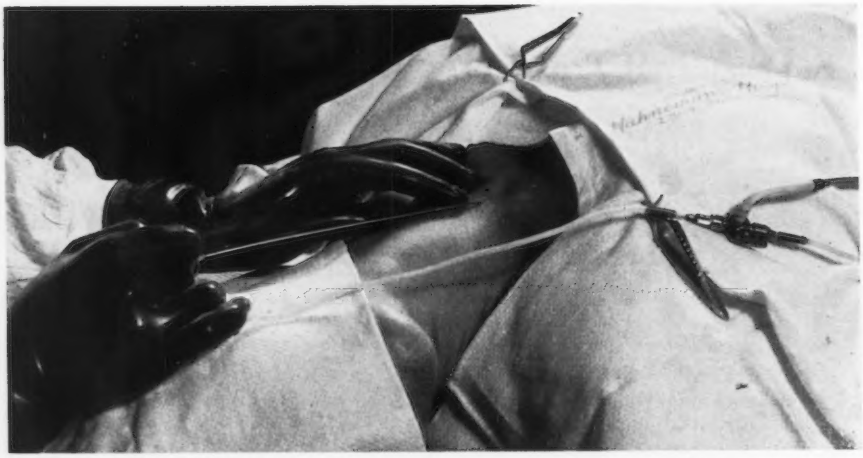

FIG. 1. Position of head and neck, and direction of needle insertion.

cock to an electromanometer and to a pressure injection apparatus. Electrocardiographic and pressure tracings are recorded on a direct-writing oscillograph. Serial filming is performed at the rate of 2 films per second for 4 to 5 seconds. In this series we employed 90 per cent sodium diatrizoate methylglucamine (Hypaque) in doses of 35 to 40 ml. per injection.

The patient is placed in supine position, with head and chin in complete extension and rotated to the right, the head actually being suspended over the filming device. From films obtained with the patient in this position, and from conventional preliminary chest films, the position of the ascending aorta, the approximate level of the aortic valve, and the most suitable roentgenographic factors are determined.

The patient is given 100 mg. of pentobarbital by mouth 1 hour prior to the procedure, followed ½ hour later by 50 mg. of meperidine, hypodermically.

At the site of needle insertion, we apply cutaneous procaine anesthesia and extend it subcutaneously below the level of the suprasternal notch. With a continuous dribble of saline solution flowing through the needle, the needle is introduced through a cutaneous stab wound approximately 3.0 cm. above the suprasternal notch. The saline dribble is then shut off and the electromanometer is adjusted to record pressure waves. The needle is passed in the midline behind the manubrium toward the ascending aorta (fig. 1). With continuous electrocardiographic recording, the needle is advanced until pressure tracings indicate aortic penetration. If there is no damping of pressure tracings, the needle is advanced a predetermined distance to place its tip slightly above the level of the aortic sinuses. If damping of pressure waves occurs, the needle is readjusted, retracted, or completely withdrawn.

With the needle in satisfactory position, and with no damping of pressure recordings, the stopcock is then adjusted to connect the needle to the injection apparatus, the patient is told to stop breathing, and the radiopaque medium is injected in approximately 2 seconds. On completion of injection, the needle is immediately withdrawn. The first of the filming series is started immediately before injection.

ANALYSIS OF CASES

Of the 31 patients 23 were males and 8 females; their ages varied from 31 to 58 years. Of the total of 35 attempts at coronary visualization, opaque medium was injected in all but 3. In these 3 instances no opaque medium was injected because of failure to obtain satisfactory needle puncture of the ascending aorta. In 1 additional case, the needle was believed to be in the ascending aorta; however, film study revealed it to be actually in the main pulmonary artery and this latter vessel was unintentionally opacified.

Of the 31 injections of opaque substance into the aorta, satisfactory needle puncture of the ascending aorta was accomplished with 1 needle pass in 20; in 5 instances satisfactory placement of the needle required 2 passes; in 3, 3 passes were required; in 2, 4 were necessary; and in 1 examination, satis-

factory placement of the needle necessitated 7 passes. Of the 11 examinations requiring more than 1 needle insertion, the pulmonary artery (as judged by the pressure wave recordings) was entered on 2 occasions.

Of the total of 31 patients, 4 had repeat examinations. One repetition was because of failure to puncture the aorta satisfactorily the first time. In another patient, the second study was performed after surgical implantation of the internal mammary artery into the myocardium (Vineberg procedure), in order to evaluate the patency of the implanted internal mammary artery. In a third patient, the second examination was performed because marked dilatation of the ascending aorta resulted in such dilution of the opaque solution that the coronary arterial system was poorly opacified; the procedure was repeated with a larger amount of opaque solution. In the fourth patient the injecting syringe collapsed at the first examination with delivery of insufficient opaque solution.

The primary purpose of the procedure was the visualization of the coronary arterial system in 23 of the 35 examinations. In 11 examinations the principal objective was the quantitation of aortic insufficiency; in 1 study, the main objective was to demonstrate a suspected patent ductus arteriosus. In the patients who had clinical features suggestive of coronary artery disease, the examination was performed to demonstrate whether the proximal portions of the coronary arteries were involved by atheromatous narrowing or occlusion.

Our procedure does not permit simultaneous multiple electrocardiographic leads; so lead II was routinely used. Of the 31 injections of radiopaque medium into the aorta, 14 showed no change in the electrocardiogram throughout the procedure. At the time of needle insertion into the aorta, there were 7 instances of electrocardiographic changes: 1 instance of sinus tachycardia, 1 of a single ventricular premature contraction; in 1, 3 ventricular premature beats; 2 instances of several atrial premature beats; 1 occasion of short runs of both atrial and ventricular tachycardia; and 1 occasion of RS-T segment elevation. Immediately at the injection of opaque medium, there were 3 occasions of minimal T-wave inversion; 1 instance of a single ventricular premature beat, and 1 occasion of sinoatrial block which persisted for 10 minutes. In the period after injection, we observed 9 occasions of sinus tachycardia, all of short duration. Several seconds of sinus bradycardia frequently preceded the tachycardia. There were also 1 occasion of a single ventricular premature contraction in the post-injection period, 1 instance of RS-T segment depression for 3 minutes, and 3 instances of T-wave inversion, lasting 1 to 5 minutes.

The most common subjective reaction was a sensation of heat and flushing. Occasionally, nausea and, less frequently, vomiting occurred. Such reactions were temporary, rarely lasting more than 60 seconds, and in no instance were they alarming. Mild headache, lasting no more than a half hour, occurred 4 times. There has been 1 episode of slight hypotension following injection of the radiopaque medium.

No clinical manifestations occurred suggestive of cerebral dysfunction or damage. In no case, to our knowledge, did the procedure precipitate a myocardial infarction or an anginal episode. The majority of patients complained of slight to moderate substernal discomfort, usually lasting less than 24 hours. In a few patients, this was present for several days and 1 patient complained of discomfort for 1 week. We have encountered 1 instance of pneumothorax. In this patient, we attempted 3 needle passes to the aorta, without success. No opaque medium was injected. The patient developed hypotension, and x-ray revealed a small pneumothorax on the right. There was no known instance of needle laceration of the aortic sinuses, the aortic valve, or the coronary artery.

In 2 patients the films revealed that a very small amount of the radiopaque medium, estimated as no more than 1.0 ml., entered the right lateral aortic wall at a point about 3.0 to 5.0 cm. above the aortic valve. The needle tip was very close to the intima of the aorta, and it is believed that this amount of opaque material was injected into the aortic wall.

Additional films taken approximately 10 and 12 minutes after the injection revealed no residuum of opaque substance in the aortic wall and we presume that it had been absorbed. No complications developed as a result of these minimal intramural injections.

Of the 31 patients in the series cardiac surgery was performed at some time following the procedure in 18. In these patients the surgical exposure afforded an opportunity to determine whether there was gross hemorrhage, hematoma, or ecchymosis of the anterior mediastinum. The time lapse between coronary arteriography and surgery ranged from 4 to 15 days. Ecchymosis of the anterior mediastinal tissues was observed in 3 instances.

In analyzing the final radiologic observations, we have graded the degree of opacification of the ascending aorta and the aortic sinuses, and of the right and left coronary arteries on a basis of excellent, good, fair, or poor opacification, or failure of opacification. In the grading we have evaluated the adequacy of visualization of the main coronary arteries and the major branches arising from each of the coronary arteries. While we are concerned with the tertiary or smaller branches of the coronary arterial system, it is well established that these branches are subject to considerable normal variation in origin, number, size, and distribution.[13] We have therefore confined our evaluation largely to the degree of visualization of the main coronary arteries and their major branches.

Seven of the 35 procedures are excluded from analysis of coronary opacification because of unsatisfactory puncture of the aorta in 3, inadvertent injection into the main pulmonary artery in 1, failure of radiographic apparatus in 2, and breaking of the injecting syringe in 1.

Thus 28 examinations remain for analysis. Opacification of the ascending aorta and aortic sinuses was considered excellent in 20, fair in 4, and poor in 4 examinations, and there were no failures. Opacification of coronary arteries was graded for the *right* coronary artery as excellent in 7, good in 3, fair in 4, poor in 3, and no opacification in 11; and for the *left* coronary artery as excellent in 3, good in 7, fair in 8, poor in 5, and no visualization in 5. There were 6 instances of opacification of the left but no opacification of the right coronary artery and 5 occasions in which neither coronary artery was opacified.

The findings of coronary arteriographic study were compared with surgical observations of the coronary arteries in 13 patients in our series. Seven of these patients were subjected to internal mammary artery implantation into the myocardium (Vineberg procedure), 5 had aortic valvular surgery, and 1 had a coronary endarterectomy. While digital and visual examination of the coronary arteries at surgery has definite limitations, it can reveal instances of atheromatous calcific change in the epicardial coronary vessels. There was essential agreement and good correlation in 8, and partial agreement in 4 cases. In 1 case there was poor arteriographic visualization of both coronary arteries, but apparently normal coronary arteries were reported at surgery. This case had marked aortic regurgitation, which probably accounted for the poor coronary opacification.

A brief description of the arteriographic and surgical findings in each of these 13 patients follows.

Case 1

Male, age 58 years. Clinical diagnosis: Aortic stenosis and coronary insufficiency.

Coronary Arteriograms. Moderate aortic regurgitation. Right coronary artery: Fair visualization, no evident lesion. Left coronary artery: Fair visualization; irregular narrowing, main trunk and anterior descending and circumflex branches, with terminal poor filling.

Surgery. Transventricular aortic commissurotomy. Severe atherosclerosis of left coronary artery and major branches.

Comment. Good correlation of coronary arteriography with surgical and subsequent autopsy findings.

Case 2

Male, age 37 years. Clinical diagnosis: Myocardial infarction, 3 years prior to admission. Progressive angina, 14 months.

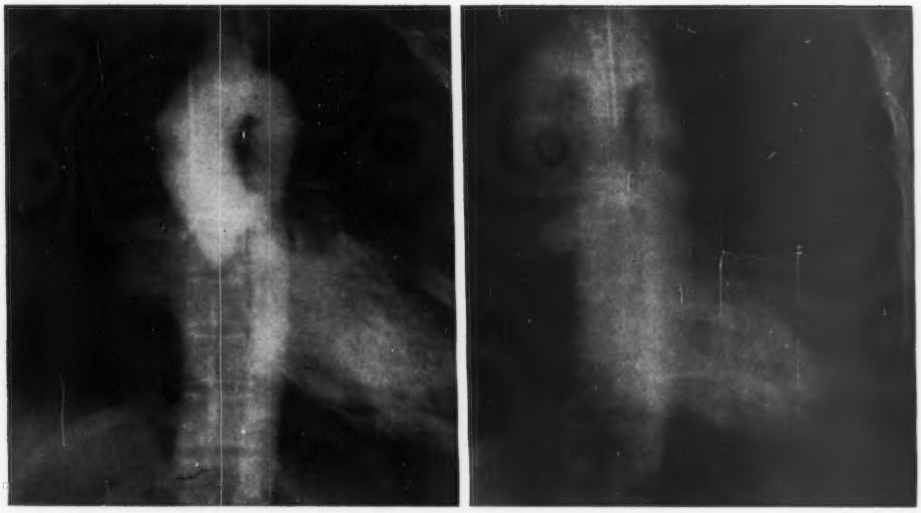

FIG. 2 *Left.* Case 4. Marked aortic regurgitation. Right coronary artery: poor visualization, no evident lesion. Left coronary artery: good visualization, no evident lesion.

FIG. 3 *Right.* Case 6. Marked aortic regurgitation. Right coronary artery: poor visualization, no evident lesion. Left coronary artery: poor visualization, no evident lesion.

Coronary Arteriograms. Right coronary artery: Good visualization, no evident lesion. Left coronary artery: Good visualization. Constrictive defects, proximal portion of anterior descending branch. Narrowing of circumflex branch.

Surgery. Attempted coronary endarterectomy, left circumflex artery, technically difficult and incomplete. Vineberg procedure: Localized sclerotic calcific lesion, proximal portion of circumflex branch of left coronary artery; anterior descending branch fibrotic and stringlike, with numerous arteriosclerotic plaques.

Comment. Good correlation of coronary arteriography with surgical findings.

Case 3

Male, age 41 years. Clinical diagnosis: Angina, 3 years, myocardial infarction, 6 months prior to admission.

Coronary Arteriograms. Right coronary artery: Good visualization. Questionable defect first centimeter. Left coronary artery: Good visualization. Extensive irregular defects, anterior descending branch. Poor filling circumflex branch.

Surgery. Vineberg procedure. Palpable sclerotic and calcific plaques, right and left coronary arteries.

Comment. Good correlation of coronary arteriography with surgical findings.

Case 4

Female, age 37 years. Clinical diagnosis: Aortic insufficiency.

Coronary Arteriograms (Fig. 2). Marked aortic regurgitation. Right coronary artery: Poor visualization, no evident lesion. Left coronary artery: Good visualization, no evident lesion.

Surgery. Open aortic annulus plication for aortic regurgitation. Normal coronary arterial system.

Comment. Partial correlation of coronary arteriography with surgical findings. Poor visualization of right coronary artery is unexplained, except on the possible basis of aortic regurgitation.

Case 5

Female, age 40 years. Clinical diagnosis: Aortic stenosis, major; aortic insufficiency, minor; cardiac failure for 14 years.

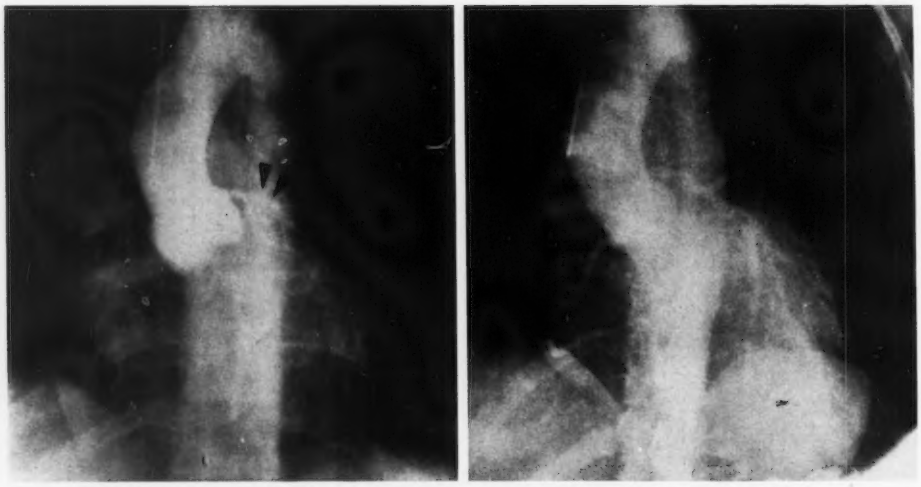

FIG. 4 *Left.* Case 10. Right coronary artery: poor visualization; incomplete filling; questionable constrictive narrowing. Left coronary artery: good visualization; constrictive defects, proximal 1.5 cm. anterior descending branch. Good visualization circumflex branch.

FIG. 5 *Right.* Case 11. Moderate aortic regurgitation. Right and left coronary arteries: excellent visualization, no evident lesion.

Coronary Arteriograms. Moderate aortic regurgitation. Right coronary artery: Fair visualization, no evident lesion. Left coronary artery: Excellent visualization, no evident lesion.

Surgery. Open aortic commissurotomy. Normal coronary arterial system.

Comment. Good correlation of coronary arteriography with surgical findings.

Case 6

Male, age 31 years. Clinical diagnosis: Aortic stenosis.

Coronary Arteriograms (Fig. 3). Marked aortic regurgitation. Right coronary artery: Poor visualization, no evident lesion. Left coronary artery: Poor visualization, no evident lesion.

Surgery. Open aortic commissurotomy. Normal coronary arterial system.

Comment. Poor correlation of coronary arteriography with surgical findings. Failure of satisfactory coronary opacification presumably due to marked aortic insufficiency.

Case 7

Male, age 40 years. History of myocardial infarction 1 year prior to admission; angina for 5 months.

Coronary Arteriograms. Right coronary artery: Good visualization, no evident lesion. Left coronary artery: Poor visualization. Questionable constrictive defect, circumflex branch. Incomplete filling of anterior descending branch.

Surgery. Vineberg procedure. Generalized coronary sclerosis, most marked in region of left circumflex branch.

Comment. Partial correlation of coronary arteriography with surgical findings. Arteriographic studies did not demonstrate sclerosis of right coronary artery.

Case 8

Male, age 56 years. Clinical diagnosis: Coronary insufficiency.

Coronary Arteriograms. Right coronary artery: No visualization. Left coronary artery: Good visualization. Irregular defects, main trunk and proximal portions of circumflex and anterior descending branches, with poor filling of distal portions of both branches.

Surgery. Vineberg procedure. Calcification, proximal portion of right coronary artery. Generalized arteriosclerotic thickening of left coronary artery and both major branches.

Comment. Good correlation of coronary arteriography with surgical findings. Nonvisualization of right coronary artery presumably due to sclerotic changes.

Case 9

Male, age 48 years. History of angina for 11 years.

Coronary Arteriograms. Right and left coronary arteries: No visualization.

Surgery. Vineberg procedure. Both coronary arteries presented extensive calcific lesions.

Comment. Good correlation of coronary arteriography with surgical findings. Nonvisualization of coronary arteries at arteriography presumably due to extensive disease of both vessels.

Case 10

Male, age 40 years. History of angina for 16 months. Myocardial infarction 1 year prior to admission.

Coronary Arteriograms (Fig. 4). Right coronary artery: Poor visualization. Incomplete filling. Questionable constrictive narrowing. Left coronary artery: Good visualization. Constrictive defects, proximal 1.5 cm. anterior descending branch. Good visualization circumflex branch.

Surgery. Vineberg procedure. Thickened proximal 2.0 cm. of right coronary artery. Thickened left main trunk and proximal 1.0 cm. of left circumflex branch. Bifurcated left anterior descending, with occlusion of mesial branch.

Comment. Partial correlation of coronary arteriography with surgical findings. Coronary arteriography did not disclose any abnormality of the circumflex branch of the left coronary artery.

Case 11

Female, age 42 years. Clinical diagnosis: Aortic stenosis, major; aortic insufficiency, minor.

Coronary Arteriograms (Fig. 5). Moderate aortic regurgitation. Right and left coronary arteries: Excellent visualization, no evident lesion.

Surgery. Open aortic commissurotomy. Normal epicardial coronary arteries.

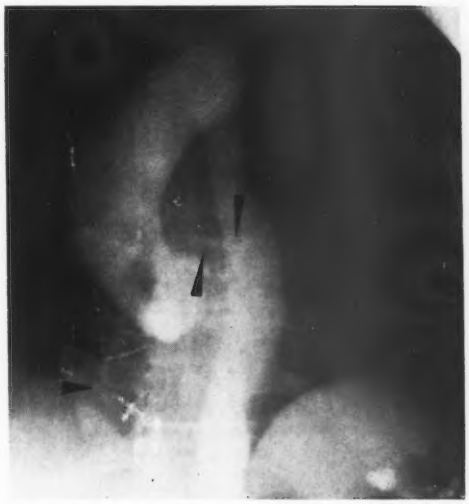

FIG. 6. Case 12. Right coronary artery: fair visualization; irregular narrowing, proximal 3.0 cm. Left coronary artery: good visualization; constrictive defects, main trunk and anterior descending branch; poor filling circumflex branch.

Comment. Good correlation of coronary arteriography with surgical findings.

Case 12

Male, age 54 years. History of angina for 8 years. Two episodes of myocardial infarction: one 8 years, and one 5 months prior to admission.

Coronary Arteriograms (Fig. 6). Right coronary artery: Fair visualization. Irregular narrowing, proximal 3.0 cm. Left coronary artery: Good visualization. Constrictive defects, main trunk and anterior descending branch. Poor filling circumflex branch.

Surgery. Vineberg procedure. Plaques in first 2 centimeters of right coronary artery. Calcific plaques in left main trunk, and in first centimeter of left circumflex branch and proximal portion of anterior descending branch.

Comment. Good correlation of coronary arteriography with surgical findings.

Case 13

Male, age 46 years. History of angina for 2 years. Electrocardiogram showed old myocardial infarction.

Coronary Arteriograms. Right coronary artery: Fair visualization. Incomplete filling. Left coronary artery: Good visualization. Irregular narrowing and constrictive defects, distal centimeter, main trunk and proximal portions circumflex and anterior descending branches.

Surgery. Coronary endarterectomy, anterior descending branch of left coronary artery. No palpable disease of right coronary artery. Sclerotic plaques in left main trunk and in circumflex and left anterior descending branches.

Comment. Partial correlation of coronary arteriography with surgical findings. The incomplete filling of the right coronary artery is unexplained.

The correlation of digital and visual surgical observations of the exposed epicardial portions of the coronary arterial system with coronary arteriographic findings raises the question of the value of each procedure in assessing pathologic states that interfere with coronary flow. The reliability of suprasternal transaortic coronary arteriography as we employ it cannot be fully determined until such time as an adequate series of cases, exhibiting no evidence of coronary artery disease by clinical history, careful clinical examination, and subsequent anatomic studies of the coronary arteries has been examined by this procedure of coronary visualization.

Summary

A procedure of coronary arteriography for needle-puncture opacification of the ascending aorta by a suprasternal approach is presented. The coronary visualizations obtained by this procedure are analyzed, and the reactions and complications encountered in 35 studies in 31 patients is recorded. The correlation of coronary arteriographic with surgical findings is discussed.

Summario in Interlingua

Es describite un technica de arteriographia coronari, con opacification acupunctural del aorta ascendente per un approche suprasternal. Le visualization coronari obtenite per iste technica es analysate, e le reactiones e complicationes incontrate in 35 studios in 31 patientes es presentate. Le correlation inter le constatationes de arteriographia coronari e le constatationes chirurgic es discutite.

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Dynamics of the Orifices of the Venae Cavae Studied by Cineangiocardiography

By Frank L. Campeti, M.D., George H. Ramsey, M.D., Raymond Gramiak, M.D., and James S. Watson, Jr., M.D.
With the technical assistance of Vivian A. Palladoro, B.S.

Closure of the caval orifices of the right atrium and dynamics of the venae cavae have been studied by an analysis of high-speed cineangiocardiographic records. The influence of respirogenic and cardiogenic factors on venae cavae dynamics was demonstrated. Findings indicated that mechanical and hemodynamic factors interact in directing the atrial blood forward and in preventing its reflux into the venae cavae. Relative narrowing of the caval orifices was demonstrated during atrial systole. The degree of narrowing, however, was insufficient to produce a mechanical closure and thus to prevent caval refluxes when the pressure gradients were altered. The findings are illustrated and discussed.

THE anatomical studies of Keith[1] demonstrated the myocardial structures of the right atrial walls and their function in closing off the venous orifices during atrial systole. Keith further postulated that under the stress of back pressure, as in the diseased heart, these myocardial bands become weak, thus producing the incompetence of the caval orifices.

The existence of such a mechanism remained controversial and lately has been denied.[2] However, recent angiocardiographic studies seem to have lent considerable support to the Keith postulates.

Hedman, Lind, and Wegelius,[3] utilizing rapid (6 to 12 exposures per second) serial angiocardiography demonstrated the systolic hesitation of contrast material at the superior caval orifice, with free entry into the right atrium during diastole. In a patient with atrial left-to-right shunt they also found, by demonstrating abnormal caval refluxes occurring during atrial systole, that the mechanism closing the inferior vena cava breaks down under stress. Campeti et al.[4] were able to show by cineangiocardiography that a similar incompetence develops at the orifice of the coronary sinus. A reflux into the coronary sinus and its tributary veins was observed during atrial systole in 88 per cent of patients with right heart hypertension.

Kjellberg and Olsson,[5] utilizing serial angiocardiography, demonstrated a narrowing of the caval and pulmonic venous orifices in both dogs and human subjects during atrial systole. They described a sphincter within the right atrial silhouette and concluded that "a sphincter mechanism is present at the junction of the caval and pulmonary veins with the auricles."

This paper is presented as a further contribution to the problem of dynamics of the caval orifices and of the venae cavae in man.

Material and Methods

Cineangiocardiographic examinations, at speeds of 15 and 30 frames per second, were made in 150 patients, undergoing investigation of congenital heart diseases, by a method previously described.[6, 7] These were studied in continuous motion as well as by single-frame projection with an analytic projector. Photographic prints and frame-by-frame tracings of the great vessels and heart chamber silhouettes offered simultaneous comparison of all phases of the mechanical cardiac cycle. Timing of the events within each cardiac cycle was made possible by Campeti's cinecardiometry,[9, 10] a method that produces curves depicting the dynamics of the various portions of the heart cham-

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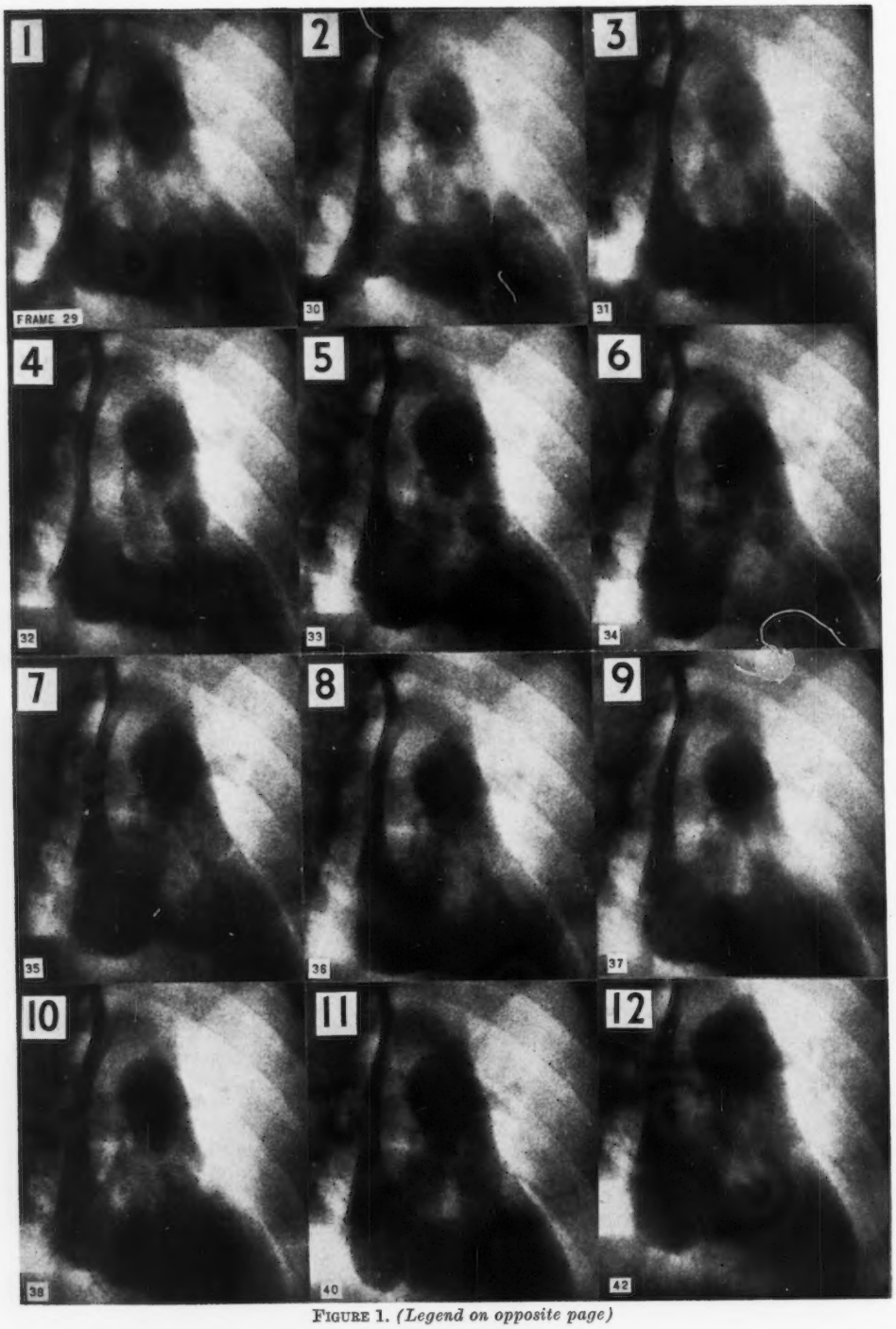

FIGURE 1. *(Legend on opposite page)*

bers and great vessels. In many cases synchronous electrocardiographic tracings were correlated with the cineangiocardiograms.

Radiologic Findings

Narrowing of the intrapericardial portion of the superior vena cava was frequently seen, as has been described by others,[3, 5] but most often during the *rapid ventricular filling* phase (fig. 1, no. *8*) During *atrial systole* the size of the vessel remained unchanged or increased (fig. 1, nos. *2* and *10*) according to the flow coming from its tributary veins and to the respiratory phase. In a few cases the sudden peripheral angiographic injection of contrast medium increased the flow and altered the normal hemodynamics.

Hedman, Lind, and Wegelius[3] published an angiocardiogram in the right anterior oblique position illustrating "narrowing of the superior vena cava simultaneously with atrial systole." However, we could identify in their serialogram not the morphology of the atrial systole but that of the rapid ventricular filling or of the diastasis, because atrium, atrial appendage, and subeustachian sinus still appeared distended while the right ventricle was partially filled. According to our findings (fig. 2), these atrial structures decrease in size during rapid ventricular filling and diastasis (early and mid-diastole) but are not altered in shape. In fact, during these 2 phases the elastic atrial walls recoil uniformly. They contract only during atrial systole. Then the characteristic silhouettes of the atrial appendage and of the subeustachian sinus suddenly decrease, deform, and cannot be identified (fig. 1, nos. *2* and *10*).

The caval flow decreases or stops at the level of the atrium when the latter is filled (fig. 1, no. *7*) immediately before the opening of the atrioventricular valves. A definite arrest of the flow also occurs during atrial systole and the following phase of isometric contraction (fig. 1, no. *10*). The flow starts again to enter the atrial cavity at the beginning of the rapid ejection phase. (fig. 1, nos. *3* and *11*).

During the period of no flow, the superior caval orifice is well opacified by contrast medium and appears funnel-shaped, with the stem directed distally and the funnel mouth at the atrial vestibulum. During atrial systole the mouth of the superior caval orifice is well marked by the decreased angiographic density of the atrial cavity (fig. 1, no. *10* and fig. 3, *C* and *D*). The marked dilution of the contrast medium by nonopaque blood coming from the inferior vena cava and from the coronary sinus is responsible for the decreased density. This borderline of the superior caval orifice in the left anterior oblique position is almost rectilinear or slightly concave downward and oblique to the external wall from the right position of atriocaval junction (fig. 4, nos. *7* and *8*) near the aortic angle. In the right anterior oblique position,

Fig. 1. Frames sequence from a right anterior oblique cineangiocardiogram recorded at 15 frames per second in a case of pulmonary valvular stenosis. These frames have been correlated with the cinecardiometric tracings shown in figure 6. The pictures show a complete cardiac cycle: *2*, atrial systole; ventricular systole: *3*, isometric contraction; *4*, *5*, ejection; *6*, end of systole; diastole: *7*, A-V valves opening, and *8*, rapid ventricular filling; *9*, diastasis; *10*, atrial systole. Atrial filling starts at the beginning of the ventricular systole and lasts until the opening of the A-V valves (*3* to *7*). The tricuspid valve ring appears outlined (*4*, *5*, *6*, *10*, *11*). The fused pulmonary valves, distended during ventricular ejection, and the hypertrophic outflow tract of the right ventricle form a mushroom-shaped silhouette (*4*, *5*, *6*, *11*, *12*). During atrial systole (*2*), at the end of the expiration (fig. 6), contrast medium refluxes into the inferior vena cava. This vessel and the atrial vestibulum between the 2 caval orifices appear distended, while the superior vena cava appears narrowed. This reflux is reversed at the beginning of ventricular systole (*3*). During inspiration (fig. 6) nonopaque blood from the inferior vena cava enters the right atrium and outlines the superior caval orifice, which is shaped like a clarinet mouth-piece (*10*, *11*). During atrial systole, atriocaval junction appears narrowed (*2*, *10*) according to the respiration phase (fig. 6).

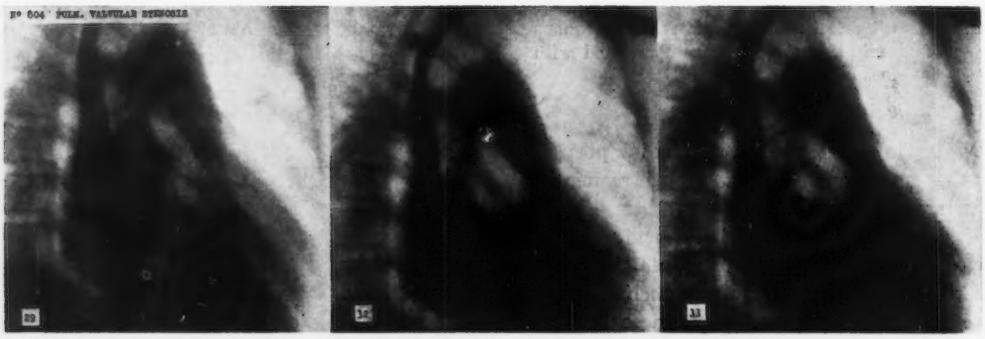

FIG. 2. Three sequential frames from 15 frames per second from a right anterior oblique cineangiocardiogram recorded in a 16-year-old patient with pure pulmonary valvular stenosis. *Left*, end systole: the atrium, atrial appendage, and subeustachian sinus are distended. The right ventricle and its outflow tract are contracted. *Middle*, ventricular filling: the atrium has decreased in size, but atrial appendage and subeustachian sinus are still visible. The ventricle is distended. *Right*, atrial systole: the atrium is contracted and the silhouettes of the atrial appendage and of the eustachian sinus are not visible. The superior caval orifice is outlined. The ventricle is fully distended, but the pulmonary artery still has the diastolic size (compare with the systolic size shown in the left picture). (These photographs have been slightly retouched.)

this borderline is slightly concave toward the right and oblique from the atriocaval junction down to the angle formed by the venae cavae. In this projection the silhouette of the superior caval orifice is shaped like a clarinet mouthpiece (fig. 1, no. *10*, fig. 2, *right*, and fig. 3, *C* and *D*). According to the anatomy of the right atrium,[1] these borderlines follow the course of the tenia terminalis contracted during atrial systole. In the extreme left anterior oblique or in lateral projections this radiologic morphology of the superior caval orifice could not be identified in our cases. However, we could demonstrate that the superior atriocaval junction was slightly narrowed during atrial systole. According to Keith,[1] this narrowing is due to the contraction of the right tenia terminalis, which passes through the anterior margin of the superior caval orifice, and of the septal band, which lies within the septal walls of the same orifice. "When the right tenia terminalis contracts it descends within the right auricle like the blade of a falchion."[1] The anterior margin of the orifice is brought downward and inward until it approaches the septal walls of the right atrium, just in front of the aortic angle. We could not demonstrate in our cases the deep sphincterial contraction closing the superior caval orifice described by Keith.[1] We think, thus, that the contraction of the right tenia terminalis and of the septal band may produce a change of the cross section of the superior caval orifice from a circle to an ellipse and a moderate decrease of the cross sectional area.

ANALYSIS OF THE CINEANGIOCARDIOGRAPHIC FINDINGS AND DISCUSSION

We analyzed the variations of the superior caval diameters on our cineangiocardiograms by a graphic method.[9, 10]

We realized that the superior vena cava[11] is a valveless and collapsible vessel, subjected to the pressure variations of the mediastinum.[12] The cross section of its mediastinal and intrapericardial portions probably varies from a circle to an ellipse[12] according to the phase of respiration and to the phase of the mechanical cardiac cycle. Although these cross sectional variations might have affected the shape of our tracings, the intimate relationship between these tracings and the phases of the mechanical and electrical cardiac cycle

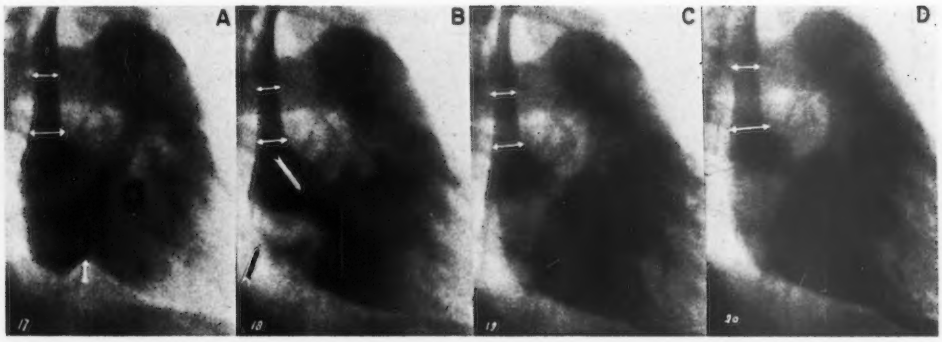

FIG. 3. Sequence showing right ventricular filling, from 15 frames per second right anterior oblique cineangiocardiogram recorded in a normal subject 15 years old. *A*. End of ventricular systole. The right atrium is filled and the silhouette of the subeustachian sinus is distended. The A-V ring is outlined. *B*. (0.066 second later). The A-V valves are opened. Atrium and superior vena cava appear decreased in size. The ventricle is partially filled. Separate streams of opaque and nonopaque blood enter the right atrium respectively from superior and inferior vena cava (*arrows*). *C*. (0.066 second later). The ventricle is filled. The flow from the venae cavae is almost arrested. The caval orifices are outlined by the angiographic density of the right atrium. *D*. (0.066 second later). End of the atrial systole. The ventricle is completely distended, the atrium is contracted, and the diameters of the intrapericardial portion of the superior vena cava are increased.

was always evident, even in the cases in which the intravenous injection of contrast medium altered the caval flow.

To represent the dynamics of different parts of the superior vena cava,[11] 3 diameters were studied: the first was traced on the extrapericardial portion immediately below the azygos vein; the second was traced at the midpoint between the azygos vein and the atrium, on the intrapericardial portion; and the third, also intrapericardial, was traced on the atrial inlet of the vein. At this level the terminal half inch of the vessel is surrounded by loops of muscular fibers. According to Keith[1] the convexities of these loops are thrown round the medial or left margin of the vessel and they terminate at the right or lateral margin near the lateral fornix of the vein.

The diameter of the atrial inlet of the superior vena cava varies synchronously and proportionately with atrial diameters and with the atrial silhouette area (fig. 5, tracing *3*). The diameter increases suddenly during the ejection phase (tracing *3*, *a-b*) corresponding to the onset of the QRS complex. At the end of the ejection phase (S-T segment) the tracing forms a small plateau (*b-c*) and then it continues to increase gradually (*c-d*) until the atrioventricular valves open (end of T wave). Afterwards the curve decreases to its lowest value (*d-e*) within the interval in which the 3 phases of the ventricular filling occur (rapid ventricular filling, diastasis, and atrial systole). On the tracing it is impossible to identify the atrial systole, in which one expects to find an indication of the contraction of the myocardial fibers surrounding the atrial inlet of the vein.

The diameter of the intrapericardial portion of the superior vena cava (fig. 5, tracing *2*), traced midpoint between the azygos vein and the atrium, presents the same characteristic variations described for the atrial inlet diameter, although of less amplitude.

The extrapericardial caval diameter (fig. 5, tracing *1*), traced immediately below the azygos vein, varies in a different pattern from that of the intrapericardial portion of the vessel. It decreases constantly after the ejection phase, corresponding to the S-T segment and the small plateau already described on

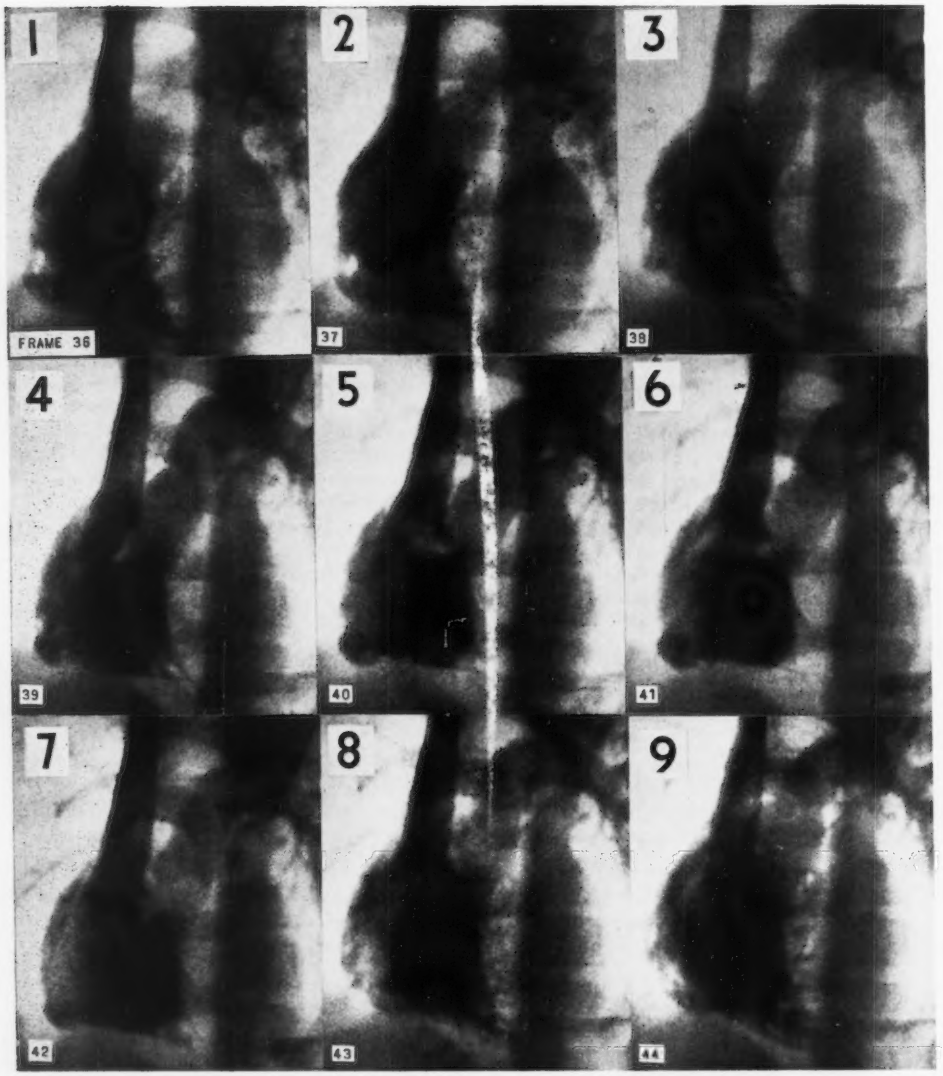

FIG. 4. Sequence from a left anterior oblique cineangiocardiogram, recorded at 15 frames per second in a case of pure pulmonary valvular stenosis. *1.* End of the atrial systole: the right atrium is contracted; the intrapericardial portion of the superior vena cava and the atriocaval junction are narrowed; the ventricle is filled and the distended outflow tract outlines the pulmonary valves still closed. *2* to *6.* Ventricular systole and simultaneous atrial filling: the caliber of the superior vena cava increases and reaches the maximum before the opening of the A-V valves *(6).* The nonopaque blood coming from the inferior vena cava produces filling defects *(4, 5, 6, 7, 8)* that outline the superior caval orifice. The fused pulmonary valves *(2, 3, 4)* appear distended. *7* to *9.* Diastole: with the opening of the A-V valves (*7*) the ventricle fills and the superior caval flow, almost arrested at the end of the systole (*6*), starts again to enter the right atrium (*7*). At the same time the caliber of the superior vena cava decreases. During atrial systole *(1, 9)* the distal portion of this vessel

(Continued on next page)

the tracing of the intrapericardial diameters (fig. 5, tracing *3*, *b-c*). Then the diameter increases until the opening of the atrioventricular valves (end of the T wave). At this point it decreases again, and the amount of decrease depends on the respiration phase and the flow of the contrast medium. Atrial and ventricular systoles are sometimes marked on the tracings by peaks of small amplitude (fig. 6), which are slightly delayed with respect to their electric manifestations (fig. 5).

This graphic analysis of the variations of the superior vena caval diameters demonstrates that the intrapericardial and extrapericardial portions of this vessel are influenced differently by respirogenic and cardiogenic factors.[12] Respirogenic factors have more influence and thus affect all portions of the vessel as well as the right atrium. During inspiration all of the superior caval diameters and the area of the right atrial silhouette increase in both systole and diastole. The reverse occurs in expiration (fig. 6). The cardiogenic factors affect directly the intrapericardial portion of the vein but influence indirectly the extrapericardial portion (figs. 5 and 6).

Recent studies[12] have demonstrated that the descent of the atrioventricular junction during ventricular systole enlarges the great venous reservoir, namely the atrium and venae cavae. The piston-like downward movement of the atrioventricular junction draws blood of the central veins into the right atrium. However, the acceleration of the venous flow during ventricular systole can be decreased by opening of the pericardium or by removing the support of the heart in other ways.[12] We therefore think of the cyclic variation of the intrapericardial pressure as an influential factor along with the cardiogenic one. This also could explain the fact that the intrapericardial portion of superior vena cava, which does not contain myocardial fibers, varies in a manner (fig. 5, tracing *2*; fig. 6, tracing *3*) similar to the area of the right atrium and to the diameter of the atriocaval junction.

In many cineangiocardiograms, normal and pathologic, in which the contrast material was injected through the vein of the arm, the reflux of medium into the inferior vena cava was observed during the atrial systole. Although the intrapericardial portion of the superior vena cava was narrowed, the intrathoracic portion of the inferior vena cava was filled and widely distended. The atrial vestibulum between the 2 caval orifices was not contracted and was clearly distinguishable from the shadows of the atrial structures (fig. 1, no. *2*). Gross observation and cinecardiometric analysis[10] (fig. 6) correlated with serial photographic enlargements (fig. 1, nos. *2* and *10*) demonstrated that the reflux into the inferior vena cava during atrial systole occurred only in expiration. In other cineangiocardiograms, in which the contrast medium was injected peripherally through the inferior vena cava, the small reflux into the superior vena cava, during atrial systole, was observed only during inspiration. This finding leads us to believe that the intrathoracic portion of the inferior vena cava is not influenced by the cardiogenic factors to the same extent as is the superior vena cava. The fact that the medium refluxes into the superior or inferior vena cava, according to the cyclic respiratory changes of the pressure gradient between these 2 vessels,[12] proves that the 2 venae cavae are in communication during the atrial systole through the atrial vestibulum (fig. 1, no. *2*) and through the narrowed but not closed caval orifices of the right atrium. The "closure of the caval orifices" or, in other

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further diminishes, the atriocaval junction narrows, and the caval orifice appears (*9*) surrounded by a band-like negative shadow. The lighter shadows produced by the outflow tract and the crista supreventricularis, both hypertrophic and still contracted during the early diastole, outline the denser silhouette of the distended sinuses of the pulmonary valves (*7*). Note, at the bottom-left of the ventricular silhouette, a round positive filling defect that increases during ventricular systole (*3* to *6*) and decreases during diastole (*7* to *9*). The true nature of this diverticular image has not yet been determined.

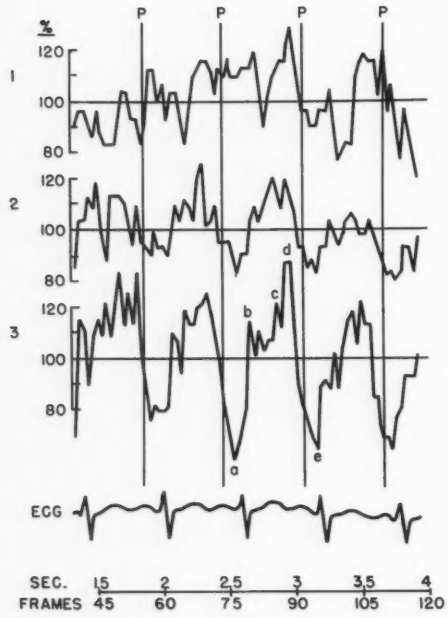

FIG. 5

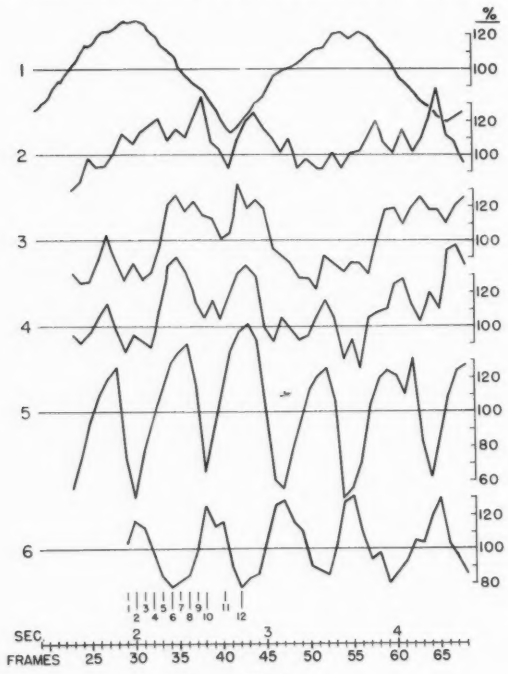

FIG. 6

FIG. 5. Caliber variation of the superior vena cava recorded by cinecardiometric method from a 30 frames per second left anterior oblique cineangiocardiogram. Caliber changes are expressed as a percentage of the arithmetrical average (base line = 100 per cent) computed by measuring at the same point the diameters in 80 consecutive frames. The tracings are correlated with electrocardiograms recorded synchronously with the cineangiocardiogram, with the time in seconds and with the frames. This figure demonstrates that the extrapericardial portion of the superior vena cava (tracing *1:* diameter traced immediately below the azygos vein) varies differently from the intrapericardial portion of the vessel (tracing *2:* midpoint between azygos vein and right atrium; tracing *3:* atriocaval junction).

FIG. 6. Right heart dynamics recorded from the same cineangiocardiogram as in figure 1. These tracings obtained by cinecardiometric method as the tracings in figure 5, are correlated with the time in seconds and with the frames. The numbers *1* to *12* on the *small scale* at the bottom correspond to the pictures in figure 1. These tracings show the influence of the respiratory phases (*1:* diaphragm movements) and of the cardiac cycle (*5, 6:* respectively areas of right atrial and ventricular silhouettes) on the extrapericardial portion of the superior vena cava (*2:* diameter traced immediately below the azygos vein) and on its intrapericardial portion (*3, 4:* diameters traced respectively at midpoint between azygos vein and atrium and at level of the atriocaval junction).

words, the forward progression of the blood during atrial systole depends upon the pressure gradient between the venae cavae and right atrium and between the right atrium and ventricle.

Concerning the mechanics of the caval orifices in preventing the regurgitation of the blood into the venae cavae during atrial systole, we cannot agree with Keith[1] and with Kjellberg and Olsson.[5] The fact that the caval orifices are surrounded by myocardial bands that contract during atrial systole, as does all of the atrial myocardium, is not a matter of discussion. The question is about the degree of narrowing. Direct radiographic signs of the contraction of these bands in cases of right atrial hypertrophy, and indirect signs produced by the characteristic stop of contrast

medium, have been observed as reported in the foregoing. However, the deep contraction which could be interpreted as a sphincterial closure of the caval orifices was not found. Nevertheless, the mechanical and hemodynamic theories of the "closure" of these orifices are not mutually exclusive.

It has been calculated[12] from a modified formula of Poiseuille's Law[13, 14] that "volume flow through partially collapsed veins obeys approximately the laws of flow through tubes of an elliptic cross-sectional area." The flow through these tubes decreases in proportion to the minor diameter of the cross section, when the pressure and the cross-sectional perimeter are kept constant. Under the same experimental conditions, a decrease of 50 per cent in the minor diameter reduces the flow to one third of that through the same tube but of circular cross section. By analogy, we believe that relative reduction of the cross-sectional area of the caval orifices and a concomitant change of the cross-sectional shape from circular to elliptic produces a zone of great resistance to the flow. This would prevent the caval reflux during atrial systole, or minimize it when the pressure gradient between right atrium and venae cavae is altered. The fact that the peripheral injection of contrast medium[15] produces a small increase in atrial pressure (1 or 2 mm. Hg) and often a reflux into the contralateral vena cava, even in normal cases, suggests that this reflux may occur also under physiologic conditions as a mechanism to prevent right atrial overfilling. The flow through superior or inferior vena cava is subject to increase suddenly in many of the daily physiologic acts that produce abrupt changes of the intrathoracic and intra-abdominal pressure. The venae cavae, then, by reciprocal shunting, act as a pressure-balancing blood reservoir for the right atrium. This should allow a gradual adjustment of the cardiac output to a sudden variation of the venous return.

Conclusion and Summary

The physiopathology of the "closure" of the venous orifices of the human right atrium has been studied in normal and pathologic cases by an analysis of high-speed cineangiocardiographic records.

Theory of myocardial sphincter-like closure and theory of functional hemodynamic closure could not be proved entirely. Mechanical and hemodynamic factors interact in closing the caval orifices during atrial systole. That caval orifices narrow during atrial systole but do not close can be demonstrated by the fact that contrast material refluxes into the contralateral vena cava during atrial systole, when, for physiopathologic causes, the gradient of pressure between the venae cavae and the atrium is altered. It is assumed by the authors that along with this relative incompetence there exists an atrial mechanism to prevent a sudden overflow from the superior or inferior parts of the body and to allow gradual adjustment of the cardiac output to the venous return.

The influence of respirogenic and cardiogenic factors on the venae cavae dynamics is demonstrated.

Acknowledgment

The authors wish to acknowledge the generous help of Dr. Lee B. Lusted in the preparation of the manuscript.

Summario in Interlingua

Le physiopathologia del "clauditura" del orificios venose del atrio dextere in humanos esseva studiate in casos normal e pathologic per le analyse de registrationes cineangiocardiographic a alte rapiditate.

Le theoria de un clauditura per action sphincteroide del myocardio e le theoria de un clauditura hemodynamic functional non poteva esser provate completemente. Factores mechanic e hemodynamic interage in effectuar le clauditura del orificios caval durante le systole atrial. Que le orificios caval se restringe durante le systole atrial sed non se claude poteva esser demonstrate per le facto que substantia de contrasto retroflue a in le vena cave contralateral durante le systole atrial quando, ab causas physiopathologic, le differentia de pression inter le venas cave e le atrio se altera. Le autores postula que—a

parte le incompetentia relative—il existe un mechanismo atrial que preveni un subite surfluxo ab le partes superior o inferior del corpore e que permitte un adjustation gradual del rendimento cardiac al retorno venose.

Es demonstrate le influentia de factores respirogenic e cardiogenic super le dynamica del venas cave.

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THE TORCH BEARERS

ALFRED NOYES
English poet, 1880-
From the Epilogue

The records grow
Unceasingly, and each new grain of truth
Is packed, like radium, with whole worlds of light.

—*Watchers of the Sky.* From *Great Companions. Readings on the Meaning and Conduct of Life from Ancient and Modern Sources.* Vol. I, Boston, The Beacon press, 1952.

Myocardial Infarction in Rats Fed Diets Containing High Fat, Cholesterol, Thiouracil, and Sodium Cholate

By WILBUR A. THOMAS, M.D., AND W. STANLEY HARTROFT, M.D., PH.D.

Investigators have produced arteriosclerosis in experimental animals by dietary means for almost half a century. In contrast to the situation in man, however, all previous reports indicate that complicating thrombosis and infarction have been extremely rare in experimental animals. The current report presents dietary regimens by means of which the authors have produced significant numbers of myocardial and renal infarcts in rats (6 of 10 in one group and 4 of 10 in each of 2 others). It is notable that thrombosis occurred before the appearance of severe structural changes in the arterial walls, although abundant fat could often be demonstrated histochemically.

FOR half a century experimental pathologists have known that arterial damage followed the feeding of cholesterol to rabbits. Within the last decade similar lesions have been produced in rats by a variety of methods, all more complex than that which suffices for the rabbit. A few reports[1-3] of isolated examples of myocardial infarction developing in animals subjected to these procedures have recently appeared. But we are unaware of any established method for the dietary production of myocardial infarction in significant percentages of experimental animals. The foregoing suggests that factors responsible for atheromatous changes in both experimental animals and man, may not be identical with those responsible for the complications of the disease—coronary arterial thrombosis and myocardial infarction.[4]

For several years we have investigated factors influencing the clotting mechanism, particularly those concerned with clot lysis.[5-8] Also, we have emphasized[9] the need for an experimental model for studying mechanisms not only for changes in arterial walls but also occlusive thromboses. With this object, an attempt was made to combine a number of conditions which together might produce arterial damage *and* occlusion with infarction. Although the experiments were not adequately controlled in all respects, results sufficiently approximate the objective to report them here.

METHODS

Seventy male rats (Wistar albinos) initially weighing 120 Gm. were placed in 7 groups. They were housed in individual, wire-bottom cages and offered water ad libitum. All were weighed twice weekly (table 1). Each day food not consumed was weighed and discarded, and measured portions of fresh diet were placed in sterilized glass containers. Records of daily food consumption of each animal were thus obtained. Pair feeding on either a food-weight or body-weight basis was not carried out, all rats being offered more than they would eat. Animals that died were refrigerated until autopsied, usually less than 12 hours after death. After 18 weeks, all survivors were killed under ether anesthesia and autopsied.

Diets. Seven semisynthetic diets were prepared according to table 2. Dry ingredients were thoroughly blended in a Hobart food mixer. Various supplements as listed were mixed in a mortar with small portions of dry ingredients and blended with the remainder in the mixer. Fats were added last; and if solid, they were warmed at room temperature until liquid. Diets were kept in tightly stoppered plastic containers and refrigerated at 4 C. for no longer than 2 weeks. Under these conditions, even high-fat diets did not become rancid.

Microscopic Studies. Sections of major viscera and vessels were placed in either cobalt-formalin* (1 to 2 weeks) or Bouin solution† (24 hours).

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*Cobalt nitrate, 1 Gm.; calcium chloride, 1 Gm.; concentrated formaldehyde (37 per cent), 10 ml.; distilled water, 90 ml.

†Saturated aqueous picric acid, 75 ml.; concentrated formaldehyde (37 per cent), 25 ml.; acetic acid (glacial), 5 ml.

TABLE 1.—*Average Weights of Rats at Biweekly Intervals**

Group No.	Week 0	2	4	6	8	10	12	14	16	18
I	105	109	124	121	119	119	116	112	116	112
II	106	95	114	115	112	114	113	103	103	108
III	104	106	119	117	116	121	120	116	116	121
IV	105	105	131	129	130	124	113	124	124	126
V	104	105	123	117	116	115	109	108	109	113
VI	106	78	83	78	73	72	74	—	—	—
VII	105	76	68	63	—	—	—	—	—	—

*All rats were weighed twice each week, but the biweekly weight record above provides a general view of the weight curves.

Hearts, kidneys, and aortas (fixed in formalin) were sectioned with a freezing microtome and stained to demonstrate abnormal deposits of fat by Wilson's modification of Lillie's supersaturated isopropanol oil red O technic.[10] Selected paraffin-embedded blocks of hearts and kidneys were sectioned serially and stained by a combined aldehyde-fuchsin-van Giesen technic for demonstration of elastic tissue and collagen. Other special stains were employed as needed, including those demonstrating ceroid and iron.

Levels of cholesterol in the plasma of most animals that survived until the end of the experiment were measured by the method of Pearson, Stern, and McGavack[11] and are reported in table 3.

RESULTS

Within the first 3 or 4 weeks most animals lost weight (table 1) and several died (table 3) presumably from thiouracil intoxication. Three rats (1 each from groups I, III, and V) lost most of the hair from their backs and flanks, suggesting an essential fatty acid deficiency state. Only one of these had a myocardial infarct. The total number of rats that developed cardiac and renal infarcts or both are listed in table 3. Other findings at autopsy included fatty livers, bronchopneumonia and, in 2 cases, pyelonephritis with multiple abcesses in liver and mediastinum. Hemorrhagic renal necrosis[12] was responsible for early deaths in animals of group VI (high fat, low protein, low choline).

Cardiac Infarcts. When present, cardiac infarcts were grossly visible on anterior aspects and apices of left ventricles. They were yellow or white and sometimes outlined by hyperemic borders between normal and damaged muscle. Infarcted areas were thin and frequently covered by attached mural thrombi that sometimes nearly filled the entire left ventricular chambers (fig. 1). Dissections of coronary arteries of these tiny hearts were not attempted lest recent thrombi be dislodged and lost.

Renal Infarcts. They were easily seen in situ and were yellow or yellow-white areas situated on lateral margins, extending anteriorly and posteriorly toward hilar regions, sometimes involving entire poles. On cut surfaces they were classically wedge-shaped with apices toward the hilum and bases at outer surfaces.

Splenic infarcts were not found in any animal. Brains were not examined. Fatty livers were regularly encountered.

Microscopic Studies. Cardiac infarcts found in these rats were morphologic duplicates of those regularly encountered in man (fig. 2). Characteristic subepicardial layers of muscle in infarcted regions are often normal. Junctions between dead and normal muscle were sharply defined by varying degrees of infiltration by inflammatory cells (fig. 3). Mural thrombi were invaded by endothelial cells, mononuclear cells, and young fibroblasts. Extent of organization of intraventricular thrombi was variable but always sufficient to indicate clearly their antemortem character (fig. 4). Deposits of neutral fat and cholesterol were abundant in subendocardial positions. Fatty degeneration was evident throughout all portions of infarcts (fig. 5).

In frozen sections, abnormal deposition of large amounts of stainable fat was often present throughout all layers of walls of coronary arteries (fig. 6). Deposition of abnormal lipid was demonstrable in almost every section of arteries in rats of groups, V, VI, and VII, and to lesser degrees in other groups. Fatty deposits in intimal, subintimal, and inner medial zones of aortas paralleled in extent those in coronary arteries. Mural plaques, fibrous intimal thickening, medial fibrosis or necrosis were not demonstrated in any arteries of rats. Absence of structural

(as distinguished from histochemical) changes deserves emphasis.

Serial sections were made of hearts in which infarcts were discovered; in some we could demonstrate short segments (0.2 to 0.5 mm.) of coronary arteries occluded by antemortem thrombi. They were composed of masses of disintegrated red cells, fibrin, and platelets invaded by large plump cells (of endothelial origin?) exhibiting many characteristics of young fibroblasts (fig. 7). At sites of thromboses vessel walls were not abnormal but for extensive deposits of stainable fat as previously described.

Sections of renal infarcts closely resemble those of man. Coagulative necrosis (fig. 8) of tubules and glomeruli left only typical "ghost" outlines of their originals. At zones of demarcation between dead and normal tissue, congestion and inflammatory cell infiltration (neutrophils) were present. Occlusive thrombi were found in major branches of renal arteries that supplied some of the infarcted regions. But in these sites structural alterations again were not evidenced and the only abnormality was deposition of stainable fat (fig. 9).

Livers contained extensive deposits of stainable fat including cholesterol. In those rats that died early in the experiment, lipid distribution was periportal, but in those that survived longer, every portion of every lobule contained fat. In animals killed at the end of 14 weeks, early periportal fibrosis was present.

Thyroid glands had undergone typical hyperplasia with papillary formation of epithelium and increased cellularity characteristic of thiouracil administration. Other organs, including adrenal glands and spleens, were unremarkable (except for excess lipid).

Discussion

The factors responsible for myocardial infarction in rats were not apparent from the experimental design employed. It is not even clear why cardiac and renal infarcts developed at all, in view of reports of similar experiments, previously conducted by others, in which only pathologic changes in arterial walls were found and no occlusion by thrombi.

Protein levels in the diets were not significant as infarcts developed in as many rats in groups fed food mixtures containing 20 per cent protein as those fed diets containing 12 per cent. Variations in carbohydrate content of the 7 diets cannot be correlated with results. Of probable significance were quantity and type of fat, and supplements of choline, thiouracil, cholesterol, and sodium cholate.

Table 2.—*Ingredients in Diets (Percentage by Weight)*

	Group No.						
	I	II	III	IV	V	VI	VII
Casein	20.0	20.0	20.0	20.0	20.0	6.0	6.0
Alpha soya protein	0	0	0	0	0	6.0	6.0
Sucrose	50.5	50.7	49.7	20.5	20.5	27.7	28.7
Salt mix*	4.0	4.0	4.0	4.0	4.0	4.0	4.0
Alphacel	6.0	6.0	6.0	6.0	6.0	6.0	6.0
Vitamin mix†	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Propylthiouracil	0.3	0.3	0.3	0.3	0.3	0.3	0.3
Choline chloride	0.2	0	1.0	0.2	0.2	1.0	0
Sodium cholate	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Corn oil	10.0	10.0	10.0	20.0	0	0	0
Butter	0	0	0	0	40.0	0	0
Lard	0	0	0	0	0	40.0	40.0
Crisco	0	0	0	20.0	0	0	0
Cholesterol	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Totals	100.0	100.0	100.0	100.0	100.0	100.0	100.0

*This salt mixture is the Wesson modification of the Osborne and Mendel salt mixture.[13]

†Each kilogram of the vitamin mixture contained the following triturated in dextrose:

	Gm.
Vitamin A concentrate (200,000 units/Gm.)	4.50
Vitamin D concentrate (400,000 units/Gm.)	0.25
Alpha tocopherol	5.00
Ascorbic acid	45.00
Inositol	5.00
Menadione	2.25
P aminobenzoic acid	5.00
Niacin	4.50
Riboflavin	1.00
Pyridoxine (hydrochloride)	1.00
Thiamine (hydrochloride)	1.00
Calcium panthothenate	3.00
Biotin	0.02
Folic acid	0.09

FIG. 1. Opened left ventricle of a rat with a large mural thrombus overlying a myocardial infarct. × 3.

FIG. 2. Section of a heart from a rat stained for fat to accentuate an infarcted area involving the apex of the left ventricle and extending into the lateral wall and interventricular septum. The right ventricle is spared. Oil red O. × 8.

FIG. 3. Myocardium of a rat, from the edge of an infarct showing relatively normal myocardium adjacent to necrotic myocardium with many inflammatory cells. Hematoxylin and eosin. × 100.

FIG. 4. Myocardial infarct at apex in a rat with an overlying mural thrombus. As in man, the mural thrombi in rats are often not firmly attached to the heart and become separated easily in processing. Aldehyde fuchsin-van Gieson. × 8.

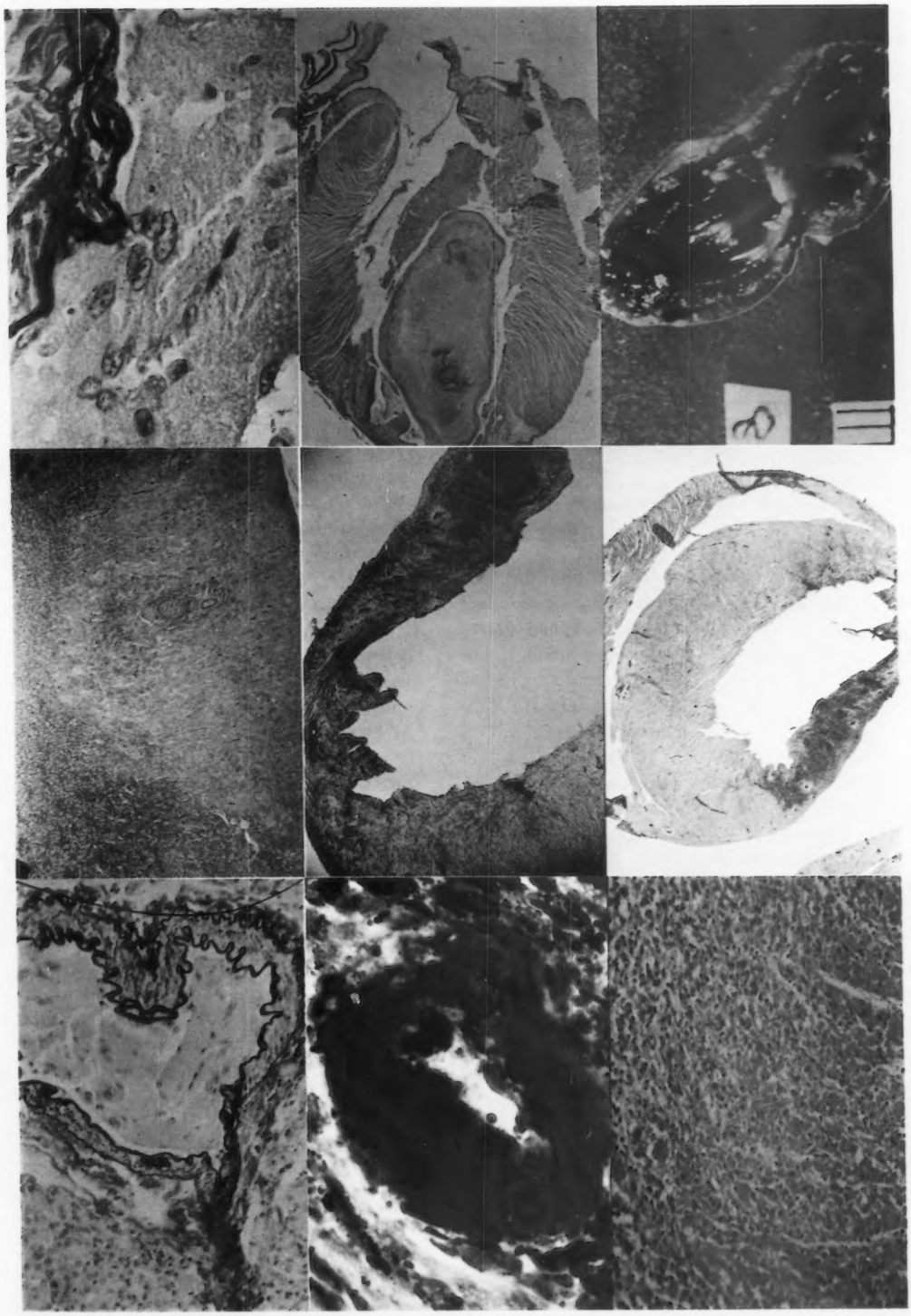
FIG. 5. Apical myocardial infarct involving almost the entire thickness of the wall. Oil red O. × 40.

FIG. 6. Small coronary artery from a rat showing a large amount of fat in all coats. The amount of stainable fat varied from that shown here to none. Oil red O. × 600.

FIG. 7. Thrombus in a coronary artery (higher magnification) of another rat that had a myocardial infarct. Aldehyde fuchsin-van Gieson stain. × 400.

FIG. 8. Renal infarct in a rat. Hematoxylin and eosin. × 40.

FIG. 9. Organizing thrombus in a renal artery of a rat that had a renal infarct. Note again (as in the heart) the absence of structural abnormalities of the arterial wall, although some fat had probably been present before processing. Aldehyde fuchsin-van Gieson. × 100.



The greatest number of infarcts were developed in animals fed large quantities of either butter or lard along with the cholesterol-elevating regimen (sodium cholate, etc.). But an equally high level of less saturated fat (20 per cent corn oil and 20 per cent Crisco) did not have the same effect and may even have afforded protection against the thiouracil, cholesterol, and bile salt. Thus, high levels of butter or lard potentiated the tendency of the diets to produce infarcts. The effects of lipotropic supplements is less clear. Although only 0.2 per cent choline was added to the diet of group V (high in butter) in which almost as many infarcts developed as in group VI (high in lard) given 1 per cent choline, the total available lipotropic content of the 2 diets was probably comparable. Adding 0.2 per cent choline to a diet containing 20 per cent casein makes its lipotropic activity not less than that of a diet containing only 6 per cent casein and 6 per cent soya protein supplemented with 1 per cent choline. Thus it appears from the results with groups V and VI that the lipotropic supplements did not protect the animals from myocardial injury and may even have potentiated development of lesions in some manner. The supplement of choline chloride was varied in groups I, II, III (all receiving 10 per cent corn oil as their only fat) from 0.0 to 0.2 to 1.0. Four of the 30 rats in these groups developed infarcts; all were in group III receiving a 1.0 per cent choline supplement. However, the numbers are probably insufficient to warrant further conclusions regarding the effect of lipotropic substances.

Essential fatty-acid deficiency may be a factor in the production of myocardial infarction in our rats. The fact that a few rats developed signs strongly suggesting essential fatty-acid deficiency may indicate that others were deficient to a lesser degree. We are further investigating this aspect in other experiments, but at present no conclusions are warranted.

Experiments are in progress for attaining a clearer evaluation of all factors. Until their results are available, the only conclusion permissible is that adequate levels of protein, minerals, and vitamins including choline, plus generous amounts of saturated fats of animal origin incorporated in diets containing thiouracil, cholesterol, and cholic acid, will, when fed to rats, produce in many of them myocardial infarcts.

TABLE 3.—*Incidence of Myocardial and Renal Infarcts*

Group No.*	No. of rats surviving	Rats surviving to end†	Average cholesterol levels‡	No. with myocardial infarcts	No. with renal infarcts	No. with either or both
I	9	8	1225(7)	0	0	0
II	9	5	830(4)	0	0	0
III	10	7	2430(5)	2	2	4(40%)
IV	9	5	980(3)	0	0	0
V	10	2	3360(2)	4	3	6(60%)
VI	7	0	—	3	2	4(40%)
VII	3	0	—	1	0	1(10%)
Totals	57	27	—	10	7	15

*Initially, each group contained 10 male rats.

†All surviving rats were killed after 131 days on specified diets.

‡Cholesterol levels in the plasma were determined at the end of 131 days on the number of rats indicated in parentheses.

The absence of structural changes in arterial walls at sites of thrombosis is of considerable significance. It reinforces our earlier suspicions that arterial plaques may not be essential in the pathogenesis of coronary occlusion, although their formation may play a part in determining sites of intravascular clotting and may enhance their formation. Experiments previously reported by us[5–8] establish that butter(and probably other saturated fats of animal origin) may affect profoundly the fibrinolytic properties of blood in vivo and in vitro. In the experiments reported herein, both coagulation and fibrinolysis of the animals' blood may have been altered significantly by the various dietary regimens, so that formation and persistence of intravascular clots were favored.

The method outlined may prove useful in studying, in experimental animals, the problem of prevention or treatment of heart disease in man. The resulting investigations

may provide at a later date information of more practical value, but at the present time our results have no application to this major problem.

Summary

Cardiac and renal infarcts resulting from intravascular thromboses in fatty, but otherwise normal, arteries occurred in as many as 60 per cent of rats fed various dietary regimens in groups of 10. The infarcts closely resembled cardiac and renal infarcts in man.

Several dietary factors were employed and inadequately controlled in these experiments, so that evaluation of their roles in production of myocardial infarction is difficult. But diets containing thiouracil, cholesterol, cholic acid, and 40 per cent butter or lard when fed to rats produced infarcts within 4 to 14 weeks.

The method should prove useful for further study of diet in relation to cardiovascular disease.

Summario in Interlingua

Infarctos cardiac e renal resultante ab thromboses intravascular in grassiose sed alteremente normal arterias occurreva in usque a 60 pro cento del rattos in gruppos decadic mantenite a varie regimes dietari. Le infarctos resimilava fortemente infarctos cardiac e renal in humanos.

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THE DISCOVERY AND EARLY DEVELOPMENT OF ANTICOAGULANTS: A HISTORICAL SYMPOSIUM

Guest Editor: IRVING S. WRIGHT, M.D.

Introduction

By IRVING S. WRIGHT, M.D.

"AT EVERY CROSSWAY on the road that leads to the future, each progressive spirit is opposed by a thousand men appointed to guard the past. Let us have no fear lest the fair towers of former days be sufficiently defended. The least that the most timid among us can do is not to add to the immense dead weight which nature drags along.

Let us not say to ourselves that the best truth always lies in moderation, in the decent average. This would perhaps be so if the majority of men did not think on a much lower plane than is needful. That is why it behooves others to think and hope on a higher plane than seems reasonable. The average, the decent moderation of today, will be the least human of things tomorrow. At the time of the Spanish Inquisition, the opinion of good sense and of the good medium was certainly that people ought not to burn too large a number of heretics; extreme and unreasonable opinion obviously demanded that they should burn none at all.

Let us think of the great invisible ship that carries our human destinies upon eternity. Like the vessels of our confined oceans, she has her sails and her ballast. The fear that she may pitch or roll on leaving the roadstead is no reason for increasing the weight of the ballast by stowing the fair white sails in the depths of the hold. They were not woven to molder side by side with cobblestones in the dark. Ballast exists everywhere; all the pebbles of the harbor, all the sand of the beach, will serve for that. But sails are rare and precious things; their place is not in the murk of the well, but amid the light of the tall masts where they will collect the winds of space."

These timeless words are from "Our Social Duty" by Maurice Maeterlinck.

This Symposium has been developed as a tribute to those who did not concern themselves with the past but who pressed forward into the unknown, facing the risks of failure even after years of work, the painful criticism by those defending the past, and, when things go wrong, the self-examination that besets the investigator who works with human subjects.

We pay special tribute to Dr. Jay McLean who died on November 14, 1957, after he had come to New York to discuss with me the plans for this Symposium. He was very enthusiastic about the plan of presenting the history of anticoagulants by those who created it. History is too often written long years afterwards by others who try to recreate it from masses of papers which are usually incomplete. This results in inaccuracies, which are then perpetuated. Jay McLean not only made a basic contribution upon which the conception of anticoagulant therapy rests but he did this in 1916 while working as a student in

Professor Howell's laboratory. This should serve as a constant inspiration to successive generations of medical students.

In the selection of the contributors to this symposium, the editor was limited by the space available. While a serious effort was made to include those whose steps most significantly advanced the discovery, development, application, and evaluation of anticoagulants, it is realized that many other workers whose contributions were important regretfully could not be included as authors. References to some of their work may be found in the texts.

The authors were encouraged to write of their experiences in a personal way. Their scientific findings have all been published elsewhere and are readily available, but what impelled them in this direction, what they felt and believed as they moved ahead, this only they can tell—others can never recapture it in the same degree. The versions do not agree in all respects. This was anticipated and no attempt has been made to reconcile the differences. These are honorable men and they have told their story as they saw it. The differences are like those so common in a courtroom—the readers now and in the future will serve as the ultimate jury. It is nevertheless a profound experience to relive this exciting phase of medical history with those who made it.

The Discovery of Heparin

By JAY MCLEAN, M.D.

THE DISCOVERY of heparin came as a result of my determination to accomplish something by my own ability. Just when this motivation arose in me and what factors nurtured this determination, which was not necessarily fully developed before I went to Johns Hopkins, are difficult to date. I believe the mile posts were the death of my father, John T. McLean, M.D., when I was 4 years old, the remarriage of my mother when I was 9, the earthquake fire in San Francisco when I was 15, the letter of my stepfather when I was 22 discontinuing any further support of my studies in 1922, and a talk with my cousin, Herbert McLean Evans (my father's sister's son), on academic behavior as a student at Johns Hopkins.

I was reared without a father, and a child knows when there is no breadwinner to rely upon. My stepfather was unsympathetic to my plans for a medical education at Johns Hopkins. The earthquake and fire in San Francisco in 1906 stripped us of all accumulated assets; our house burned, my stepfather's place of employment burned, and the outlook was stark.

Despite these handicaps, I made the decision to become a physician during my last year at Lowell High School in San Francisco (1908-1909). At this time I read Flexner's *Medical Education in the United States.* I have remembered he described the "chem lab" of one school as "consisting of a cigar box of broken test tubes." I entered the University of California at Berkeley (1909), and while there firmly hitched my future to Johns Hopkins Medical School and a career in academic surgery.

At that time (1911) one could enter the University of California Medical School with two years of college preparation, but Johns Hopkins required at least three. I was forced at the end of my sophomore year, May 1911, to make the choice. My stepfather argued that the University of California Medical School had sufficed for my father (M.D. 1867) and for his 15 year old brother, Robert Armistead McLean (M.D. 1876), Professor of Surgery and Dean, Emeritus, in 1911. After his death in 1918, he was honored in the medical literature as "California's First Master Surgeon."

My argument was that Johns Hopkins offered me more preparation in the field of academic surgery, that is, research and teaching, for a lifetime career. Also I felt deeply the responsibility of being a physician. I doubted if I possessed the qualifications to become one; and I deliberately chose the fiercest student competition, as Johns Hopkins' matriculants were meticulously chosen.

My stepfather had paid for my board and room, $27.50, during my freshman and sophomore years at college; the rest I earned. He offered to continue this for four years of medical school at the University of California in San Francisco. If I had decided to go to Johns Hopkins, his aid would be stopped at the end of my sophomore year, May 1911.

Summer work would not yield enough in savings to finance my third college year, so I was forced to leave college for fifteen months. Some of my Sigma Chi Fraternity brothers were going to the Mojave Desert gold mine, The Yellow Aster, at Randsburg, for practical experience in mining engineering. I followed them—got a job as "mucker" (twenty-five cents an hour)—rose to chuck-tender, apprentice miner, and then to a mill-hand, where we processed the ore into beautiful gold bricks. I stayed there until August 1912, fifteen months in all, with enough money saved to re-enter college then for the third year of preparation for Johns Hopkins. My spare time was devoted to various part-time jobs. Robert Sproul, now President of the University of California, and I both worked in the Recorder's office. I did blood counts and urinalyses in the College Infirmary, worked in the Museum of Invertebrate Zoology, and book-stores. I also worked scrubbing the decks of ferry boats plying in San Francisco Bay

lumberyards, and as Railway Mail Clerk from Oakland to Denver. All of this was not new to me as I worked at various odd jobs since the age of twelve.

In the fall of 1913 I commenced my final year at the University of California which was concurrently my first year as a medical student, and was graduated May 1914 with a B.S. degree—but "broke" again. My ill uncle, Robert Armistead McLean, sat with the faculty on the stage of the Hearst Greek Theater. One of my subjects in the first year of medicine was physiology under Professor Maxwell. Howell's textbook was used. I was fascinated with the subject and its research possibilities. I wanted to do some research there; but all my spare time was devoted to my job as a technician in the clinical pathology laboratory at the College Infirmary.

I applied for admission to Johns Hopkins but later learned that my dean at the University of California had written the dean at Johns Hopkins that "I was not the kind of man Hopkins sought." In addition, I had no money for the transcontinental journey, let alone the expenses for an academic year at Johns Hopkins.

So I returned to remunerative labor, this time drilling oil wells. Manual labor paid so much more than "white collar jobs" and living costs were lower—hence producing greater savings for my purpose.

Again, after fifteen months of work, I had funds for one year at medical school. Even though I had been notified I was not acceptable as a student at Johns Hopkins, I bought a ticket from San Francisco to Baltimore and went there after paying off a senior class loan to the University of California.

I arrived in Baltimore one Sunday morning at Port Royall Station and trudged with my suitcase to the Washington Monument, the first to be erected to him in the United States, and to the Stafford Hotel nearby. My object in going to Baltimore, knowing that I had been rejected for admission to the second year class was twofold. I reasoned that I could work a year there as well as in California; secondly, after my 1914 graduation from the University of California, Johns Hopkins had added organic chemistry lab to lectures as a requirement for admission. Working in the oil fields, I could not acquire this subject. I calculated I could work in Baltimore and make this up at Johns Hopkins University at Homewood.

Monday, the next day, I went over to Johns Hopkins Medical School and Hospital and introduced myself to Mr. Coy, the Registrar, and to Dr. W. Williams, the Dean. Then I arranged to share a room on Biddle Street with Irwin Schumacher, now on the faculty of the University of California in San Francisco. Arnold Rich, now Professor of Pathology at Johns Hopkins, and James Cash, now Professor of Pathology, University of Virginia, were roommates next door. Mr. Coy was surprised to see me and asked if I had not received the letter denying me admission. I told him I had, but figured on working a year; and I started to look for a job. The next day word was sent to me to see the Dean. I was informed there was an unexpected vacancy and I had been admitted to the school in the second year of medicine.

I promptly paid the fees for a year as a medical student, taking no medical school courses. I immediately called on Dr. Howell and told him of my desire to prepare for an academic career in surgery and that I wished to devote one whole year to physiological research now. I felt that I could never do it after graduation for that would interfere with the house officer progress on a surgical staff. I told him then that I wanted a problem I could reasonably hope to finish and publish in one academic year entirely by myself. I wanted to determine if I could solve a problem by myself. I told him my savings would just last one year, and after that I would have to work a year before returning to school.

He gave me the problem of determining the value of the thromboplastic substance of the body. He thought this to be kephalin (cephalin), obtained from brain but, of course, knew the thromboplastic material from brain to be a mixture—a crude extract, though a powerful thromboplastic agent. He made this by macerating brain tissue, spreading it on glass panes, drying it over a gas flame in an oven, extract-

ing it in ether, decanting, concentrating the ether extract, and finally by precipitation with alcohol. This precipitate was his thromboplastic substance. He used it in blood-clotting experiments. It was kept in a glass vessel with ground glass cover (vaselined), as it was observed that access of air decreased its ability to accelerate clotting. In three months it was decayed.

My problem was to determine what portion of this crude extract was the active accelerator of the clotting process and to that end, to prepare cephalin as pure as possible and determine if it had thromboplastic action. I was also to test the other components of the crude ether-alcohol extract. I was assigned a sink and attached "table-drainboard" with a shelf over the sink in a large student physiology laboratory (not used as such then) across the hall from Dr. Howell's office and private laboratory.

Others working in the department at the time (1915) were Charles Snyder, Donald Hooker, Cecil and Mrs. Drinker, and Stanley Cobb. I was held distantly by them, except by Dr. Snyder. They, with Dr. Howell, lunched together, but I was not invited to join them. I was not a colleague. This may also have been in part because my drying tissues produced an all-pervading insufferable odor which penetrated throughout the laboratories on the floor and to Dr. Abel's laboratory on the floor above!

At the same time I started the organic chemistry laboratory course, to wipe out an entrance deficiency, and voluntarily took an advanced course in German, the better to read the German chemistry literature on lipoids. Hugh MacLean's book, however, was in English.

It was this determination to become a physiology-based surgeon rather than an anatomy-based surgeon that led to the discovery of heparin. In those days, 1912-1913, anatomy was considered the main foundation for surgery, as it had been for Robert A. McLean and my father.

My key decisions were thus as follows:

1. Study medicine.
2. Academic career.
3. Johns Hopkins.
4. Physiology.
5. Investigate the brain and other organs for thromboplastic agents.
6. Study for deterioration of cephalin.
7. Save these longer in event heparin action came up (dog experiment).

In 1915 my cousin, Herbert McLean Evans, M.D., Sc.D., moved from Johns Hopkins to the University of California as Professor of Anatomy. I met him for the first time the day before I left for Baltimore. He gave me the following advice: "Ask no questions but look up for yourself what you want to know." He gave me many letters of instruction to his friends, members of the faculty at Johns Hopkins. Except for one to Dr. Howell, I did not present them as I wanted to progress by my own efforts.

I worked nights, Saturdays, and Sundays and the first steps of my problem were completed in December 1915. I still had enough money for board and lodging until June 1916 so I could continue to work in research without receiving any stipend from the medical school. I suggested to Dr. Howell that it might be profitable to extract the lipoids (phosphatides) from many different organs. I reasoned that as cephalin could not be crystallized, one could not be sure of its purity and hence, its function as the thromboplastic substance of the body. However, if the thromboplastic activity of brain extract were due to some other substance, adherent to or absorbed by cephalin, this might not be so in organs which did not contain such a large amount of cephalin as the brain does.

In my reading of the German chemical literature on phosphatides, I found articles by Erlandsen and Baskoff in which they described extracts of heart and liver secured by a process similar to that for obtaining cephalin from brain. Therefore, these products might be heart and liver cephalin, but were named cuorin (from the heart) and heparphosphatide (from the liver): hence the name heparin. I suggested this research problem as a logical supplement to the problem Dr. Howell had given me. He had not known about cuorin or heparphosphatide.

I first prepared cuorin. The final extract was brown, not white or yellow like cephalin. It was waxy. It was a powder. It did not smell "fishy" as does cephalin and although it accelerated the clotting of blood somewhat, it was not as powerful as brain cephalin.

I then prepared Baskoff's heparphosphatide with a similar result. As in the brain, the more "purifications" done (ether extract into hot alcohol), the weaker the thromboplastic activity became. The same process of extraction was used for brain, heart, and liver, yet in the brain, the end product was almost all cephalin, but in the heart and especially in the liver it was something else which was mixed with cephalin. As cephalin is powerful, a small amount of it gives ample evidence of its thromboplastic power. Many batches were made of both cuorin and heparphosphatide. By this time, what little cephalin remained from my former studies with brain tissue was deteriorated by the process of extraction plus air and time. I was about to go on to the extraction of cephalin from the uterus and skin. I had saved batches of cuorin and heparphosphatide and from time to time tested these in serum plasma to determine whether or not the cephalin from the heart and liver deteriorated and lost its thromboplastic power as did that from the brain. If I had not saved them, I would probably not have found heparin.

This was a fortuitous decision. All I was trying to prove was that an ether-soluble, alcohol-insoluble extract of cephalin would accelerate coagulation of blood, and it did.

I became interested in the deterioration of cephalin (an unsaturated fatty acid), which I assumed became saturated on exposure to air (and ether-alcohol purification). It seemed sound to determine the iodine number of fresh cephalin in various stages of its decay down to no activity—about 3 months—by exposure to air. This Arbeit was completed and published the following year (1916-1917) at the University of Pennsylvania.

The various batches were tested down to the point of no thromboplastic activity, but two of those first prepared appeared not only to have lost their thromboplastic action, but actually to retard slightly the coagulation of the serum-plasma mixture. I had in mind, of course, no thought of an anticoagulant, but the experimental fact was before me; and I retested again and again until I was satisfied that an extract of liver (more than heart) possessed a strong anticoagulant action after its contained cephalin had lost its thromboplastic action.

At first I said nothing to Dr. Howell about this. It was not part of my planned problem, and it took time to satisfy myself. I had been working alone, in no wise assisting Dr. Howell. He was then engaged much of each day in a dark room watching precipitates of fibrin form through a microscope.

After more tests and the preparation of other batches of heparphosphatide, I went one morning to the door of Dr. Howell's office, and standing there (he was seated at his desk), I said, "Dr. Howell, I have discovered antithrombin." He smiled and said, "Antithrombin is a protein, and you are working with phosphatides. Are you sure that salt is not contaminating your substance?"

I told him I was not sure of that, but it was a powerful anticoagulant. He was most skeptical. So I had the Diener, John Schweinhant, bleed a cat. Into a small beaker full of its blood, I stirred all of a proven batch of heparphosphatides, and I placed this on Dr. Howell's laboratory table and asked him to tell me when it clotted. It never did clot.

He still did not believe that I had discovered a natural anticoagulant, but it was at this point that he became associated in my research problem, namely the study of the effects of my anticoagulating substance (heparphosphatide), which gave greater yield and higher anticoagulating potential than cuorin in vivo in dogs. When I demonstrated new batches to him in vitro, and be became satisfied that it did actually inhibit the coagulation of the serum-plasma test mixture as well as whole blood in vitro, we planned the first in vivo experiment with a dog and administered the heparin intravenously.

(This was as far as Dr. McLean progressed in his history of the discovery of heparin before he developed his fatal illness and died November 14, 1957.—Ed.)

Preparation of Heparin and Its Use in the First Clinical Cases

By CHARLES H. BEST, C.B.E., M.D., D.Sc., LL.D., F.R.S.

MANY OF US, who were friends of the late Dr. Jay McLean, had looked forward with great pleasure to seeing him again at this time and to discussing the problems which occupied so much of his attention. We all join Dr. Wright in paying tribute to Dr. McLean, the discoverer of heparin, and to Professor W. H. Howell and his colleagues, who extended this work and focused our attention on many of the most important problems in this field. A number of years ago Dr. McLean wrote to me and asked if we would take the responsibility for his collection of notes and reprints and other documents relating to heparin. I was honoured and extremely pleased to accept this invitation.

It is almost always true that a very careful search of the literature will reveal papers which anticipate, to varying degrees, the discovery of a signal advance in medical or other sciences. In 1912, Doyon[1] published a paper in which he describes an attempt to isolate and characterize an anticoagulant released by the injection of peptone in a dog. This work was interrupted by World War I. There are a number of other intriguing findings in the literature, for example that of Schmidt[2] in 1892, but their significance could only be appreciated after the discovery of heparin by Dr. McLean[3] in 1916.

On November 14, 1940, Dr. Jay McLean wrote me a long letter describing the whole history of his work on heparin, and a great deal about his subsequent researches. I will quote parts of this letter.

> You may, however, be interested to know that the first presentation of the anticoagulant at a scientific society was made February 19, 1916, before the Society of the Normal and Pathological Physiology at the University of Pennsylvania. A. N. Richards, the Secretary was then Professor of Pharmacology, and is now Vice-President of the University for the Medical Sciences. These talks were not published although the secretary may have a record in the minutes of the Society . . . Concerning the lack of articles on heparin in the literature by me, you may be interested in the following. When I wrote the paper on "The thromboplastic action of cephalin," Doctor Howell did not think that I should include anything about the discovery of the anticoagulant. He felt that this should be studied more thoroughly and a paper written about it later. I argued, however, that I had made this finding during that academic year's work in 1915-1916, and felt that it should be included as a record of the work done during that period. I felt this the more strongly because I had already accepted a Fellowship in the Department of Research Medicine at the University of Pennsylvania under Dr. Richard Pearce for the following academic year, 1916-1917 and therefore could not continue the work in Baltimore. He finally agreed to permit its inclusion in the body of the paper.
>
> . . . At first, Doctor Howell was very skeptical that I had found a true anticoagulant. You know that from my method of preparation, I was using very weak heparin and therefore its anticoagulating action was not noticed with the suddenness and brilliancy of an exploding bomb. Furthermore, you will recall that I was searching for coagulants, not an anticoagulant, and that the end point of my experiments was a clot such as is promptly and solidly formed by cephalin. It was only through very careful records, the systematic saving of the little tubes in which I tested the substances, and then repeating the experiments with the same lot of material and finally making new preparations that I gradually became aware that I had an anticoagulant. Naturally I regard the statements in the literature that I discovered this "accidentally" as not correct. It was discovered "incidentally" in the course of the problem but not "accidentally."
>
> . . . You will find in the beginning of my laboratory note-book, which I am sending you, the extent of the problem Doctor Howell outlined in his own handwriting, namely, "The preparation of pure cephalin." In looking over this note-book, will you tolerantly excuse its lack of neatness?
>
> . . . As regards the earlier studies with the anti-

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coagulant, you might be interested in the following: one author calls my attention to the fourth sentence in the first paragraph of my 1916 paper, which would give one the impression that Doctor Howell suggested that I study cuorin and heparphosphatid for their thromboplastic action. The facts are that the problem Howell originally gave me was simply to make cephalin as pure as possible from the brain and to test each fraction I separated out in the phosphatid group for its thromboplastic action. I finished most of this work between October 15 and January 1916 . . . I first prepared cuorin in January 1916, and it was in January, February and March that I established definitely its anticoagulating action, first of cuorin and then heparphosphatid. It was not until later that Doctor Howell became actively associated in work with the anticoagulant by intravascular injections and mechanism of action in vitro.

I can't think of any other material I have that might be of interest to you. May I, however, offer a suggestion which you may or may not deem worthy of mentioning in your lecture. Doctor Howell has always been perfectly clear and fair in his statements about the discovery of the anticoagulant. As the years go by, more authors credit him with the discovery, apparently disregarding my 1916 publication and the statements he made in his 1917 and 1918 publications. In his Harvey Lecture, he definitely states that this work was done by me, and in his 1918 paper you will note that he says "In the course of *his* (*that is Jay McLean's*) work, the anticoagulating action was discovered." Doctor Howell has always simply stated that he and Holt "first described" heparin.

Dr. McLean attempted several times to return to active experimental work in the heparin field but was engaged in clinical practice.

It was apparent from correspondence which I had with Dr. McLean that he had been trying to interest the United States Public Health Service and institutions in various other countries in doing something about the preservation of his notes, reprints, and other heparin memborabilia. He finally decided to send all of these historical documents to us in the Department of Physiology and the Banting and Best Department of Medical Research. The documents are now stored in the Library of The Charles H. Best Institute.

I had many friendly letters from Dr. McLean. He was most generous in his appreciation of the contribution of our group in Toronto. On May 6, 1940, the discoverer of heparin wrote, "I regard you and the work you stimulated in Toronto to have brought about the debut of heparin for clinical use." My colleagues, Arthur Charles, David Scott, Gordon Murray, Louis Jaques, and T. S. Perrett, deserve a very large share of this praise.

In 1918, Howell and Holt[4] proceeded with the extension of McLean's work. They state, "Attention was first called to this substance during some work done in this laboratory by Jay McLean," that is, to the substance heparin. Howell and Holt go on to say that they varied the methods in many different ways, and finally selected one which yielded a reliable preparation of heparin. In the copies of these articles in the McLean files, there are many interesting marginal comments; for example, Dr. McLean has pointed out that this description of his work by Professor Howell and Dr. Holt was really the first published announcement of the discovery of heparin. There are many interesting points also in Howell and Holt's paper. They introduced, for the first time, the word "heparin"; McLean had referred to these compounds carrying the anticoagulant activity as "phosphatids from heart or liver." They found that heparin could be prepared from lymph glands as well as from heart and liver, as originally shown by McLean. The antagonism between cephalin and heparin on the clotting system was described in the Howell and Holt paper. It has been questioned whether the material that Howell and Holt had was actually heparin, since it was soluble in the crude form in ether. It is now considered that it probably was heparin, since it became insoluble in ether after repeated alcohol precipitations. In 1922 and 1925 Howell[5, 6] described the preparation of heparin in more purified form and in 1928 he[7] published a detailed report on its chemical and physiologic reactions.

In 1924 Mason[8] showed that heparin would prevent the intravascular clot produced in rabbits and dogs by the injection of thromboplastin from tissue extracts. These were true clots and not platelet thrombi. In 1925 my close friend C. I. Reed[9] found that heparin was an effective anticoagulant in dogs and

was well tolerated. In 1927, Shionoya[10] reported that the administration of heparin did not prevent the agglutination of platelets when blood was made to pass through a collodion tube. Thus it seemed that heparin might be an anticoagulant but not an antithrombotic agent.

Professor Howell undoubtedly anticipated many of the developments which took place in the future. He expressed the hope that heparin would find a suitable application in experimental work and possibly in the therapeutic treatment of disorders of coagulation. Professor Howell thought it not improbable that this substance might be of physiologic significance, and in discussions on coagulation of the blood he often referred to heparin as a "physiological anticoagulant."

While working in Dale's laboratory in London in 1928 I had decided to organize a group, on my return to Toronto, to study the chemistry and physiology of heparin. Later that year, Dr. E. W. McHenry and I, eager to use an effective anticoagulant in our histaminase work, found it possible to prepare active fractions from ox liver by Howell's method. A little later I made a comprehensive study of the literature and it became apparent that very little work indeed was being done in this field. A potent anticoagulant that could be used for long continued administration in animals, was not available. No anticoagulant preparation was safe for clinical work and none was being used. In the Connaught Laboratories I had been intimately concerned with the preparation of insulin and of liver extract for administration to human patients and I visualized a similar advance in the heparin field. Progress was, apparently, also inhibited by the lack of convincing evidence that heparin inhibited platelet agglutination as well as coagulation.

It was obvious that further chemical work on the purification of heparin must precede physiologic and clinical studies. In 1929 I was able to interest a young organic chemist, Mr. Arthur Charles, in this problem, and he made some preliminary studies with me in the Department of Physiology and then joined forces with my colleague of long standing, Dr. D. A. Scott. From that time on the chemical work on heparin was conducted in the Connaught Laboratories, of which I was then an Assistant Director.

On November 10, 1931, I wrote to Professor W. H. Howell:

> I would very much appreciate your opinion with regard to several questions in connection with heparin. During the last few years we have been using great amounts of this material in physiological and bacteriological work. Quite recently, one of the junior members of the Connaught Laboratories, which, as you know, are a department in the University, has interested himself, at my suggestion, in the preparation of heparin from beef liver. He is now in a position to make fairly large amounts of the material which is at least as potent as that distributed by Hynson, Westcott and Dunning. One half gram of this material is being forwarded to you under separate cover. Would you have any objection if this material should be sold by the Connaught Laboratories? (*Now the Connaught Medical Research Laboratories whose objectives are the support of research by the sale of biological products at the lowest possible price.*) I believe that the price would be much more reasonable. As you know, there is a very high tariff on biological products going into the United States so there is very little likelihood of any interference with the American business of Hynson, Westcott and Dunning.

On November 14, 1931, I received the following reply from Professor W. H. Howell in his own handwriting.

> I am interested and pleased to know that you have got a usable preparation of heparin out of beef liver. I never could make that source give a decent preparation. As to your selling it, there can be no objection to that, of course. I have feared, at times, that the Hynson, Westcott and Dunning firm would give up its production, as they always claimed that it was a losing proposition to them, so it may be well to have another source. I have been very anxious for them to market a purified heparin, potency 1:50 in 100, but the method I gave to them makes their product too expensive, they think.

The work on heparin in the University of Toronto was the product of activity in three departments—Physiology, the Connaught Laboratories and the Department of Surgery.

Dr. David Scott and Dr. Arthur Charles[11–15] were extremely successful in their chemical work during the years 1933 to 1936. The most important and novel steps in the preparation and purification of heparin which they introduced were (1) the finding that autolysis of tissue resulted in a much higher yield of heparin, (2) the discovery that beef lung yielded almost as much heparin as liver—this made it possible to use a much cheaper source of raw material, (3) the finding that the destruction of protein by trypsin in the crude protein-heparin complex, was an extremely important factor in the further purification of the anticoagulant, (4) the preparation of a crystalline material as the barium salt—they found that this purified material was of uniform composition and potency. The Danish workers, Schmitz and Fischer,[16] had isolated in 1933 the anticoagulant material from dog's liver as the brucine salt. Neither the brucine salt nor the barium salt lent itself to any large-scale production. Somewhat later Charles and Scott were able to convert the crystalline barium salt of heparin into the sodium salt.

The labels on the bottles of heparin prepared by Hynson, Westcott, and Dunning from dog's liver by Howell's procedure, stated "1 mg. will prevent the coagulation of 5 cc. of cat's blood in the cold." Charles and Scott used this preparation as a reference standard and assigned it a potency of 5 units per mg. In terms of this material the potency of the crystalline barium salt was 110 units per mg. but for simplicity in calculation Charles and Scott decided to assign the figure of 100 units per mg. The material provided for the international standard of heparin was the sodium salt prepared from the crystalline barium salt. The potency of the international standard[17] of heparin was defined as 130 units per mg., that is, there are 130 arbitrary units of heparin per mg. of the international yardstick. It is calculated that the potency of the international standard is 28 times that of the early Hynson, Westcott, and Dunning preparation. The Connaught Laboratories in Toronto have made two international biological standards—the one for insulin and the one for heparin.

In addition to obtaining heparin in a highly purified form I thought that another point should be settled before the anticoagulant should be submitted for clinical trial. This was the ability or inability of heparin to prevent the agglutination of platelets, which is the first step in the formation of a thrombus as distinguished from a clot.

In 1929, the year after we started our work on heparin, Professor W. E. Gallie, Head of the Department of Surgery in Toronto, nominated Dr. Gordon Murray to collaborate with workers in my department, who were investigating the effects of heparin in the prevention of experimental thrombosis. I was fortunate in having in my department at that time, Dr. T. S. Perrett a Fellow from the Department of Surgery. I was also fortunate in having a pupil who was taking his doctor's degree in physiology. This student soon became a colleague in the heparin work and a very close friend. He was, as you know, Dr. Louis Jaques, who later became the Head of the Department of Physiology at the University of Saskatchewan and an international authority on many aspects of blood clotting and thrombosis. Dr. Jaques, among the other services which he rendered to our department, sent me one of his own pupils, Dr. Frank Monkhouse, who received his Ph.D. in Physiology from my department in 1952. Dr. Monkhouse is, therefore, my scientific grandson and he, in his turn, has become an authority on different aspects of the great field of blood coagulation and thrombus formation.

The work on the effect of heparin on experimental thrombosis begun in 1929, was pushed forward by Dr. Murray, Dr. Jaques, Dr. Perrett, and myself. We[18] found that the incidence of obstruction of peripheral veins in dogs by thrombi formed as a result of mechanical or chemical injuries to the intimal surfaces of the blood vessels was definitely decreased when solutions of purified heparin were administered before and for long periods following the injury. These results were obtained in studies of some 300 veins. Thrombi were not observed even after very severe

chemical injury while the animal was well heparinized. We found that the intimal surfaces of veins removed from heparinized animals several days after the injection of heparin had been discontinued appeared, on microscopic examination, to have recovered completely from the injury. The microscopic examinations revealed, in some cases, minute masses of platelets, filling small crevices in the intima. Healing was, however, complete as judged by the absence of thrombus formation after discontinuing the anticoagulant.

The experimental evidence of the prevention of thrombus formation initiated by platelet agglutination, was completely satisfactory before attempts were made to apply solutions of purified heparin to clinical problems.

At various stages in the purification of heparin attempts had been made to use the material as an anticoagulant in transfusing human patients. In 1924 Mason[19] used crude material and obtained reactions which varied from slight chills to severe headache and high fever and nausea. In 1928 Howell[7] used somewhat purer heparin and reported a slight reaction in 2 of 10 transfusions carried out on 6 patients. Godlowski[20] in 1933 reported on the use of heparin in human patients, and although he found low levels of toxicity, the preparation he used was extremely crude and of low potency. In 1936 Hedenius and Wilander[21] studied coagulation times of healthy human subjects. They found that heparin produced no ill effects when the material was given intravenously. This heparin was obtained from Dr. Erich Jorpes and was made by the Charles and Scott procedure.

The work on heparin in Toronto, begun in 1928, proceeded steadily. With each advance in purification we, Murray, Jaques, Perrett and Best, studied the effect on experimental thrombosis and Dr. Gordon Murray made clinical trials beginning in May 1935. When the crystalline sodium salt became available it proved to be safe and effective for the heparinization of patients.

On May 8, 1935, Dr. Jorpes wrote to me from Stockholm in his own hand.

> I am sending you a copy of the preliminary report about heparin, and would like to use this opportunity to thank you for all the hospitality shown to me and to Mr. Bjurling during our visit in Toronto in 1929. We have greatly benefited from your experience in the manufacture of insulin.
>
> The heparin work has been a very hard task. For a very long time I believed that my preparations were only impurities as compared with those of Charles and Scott. I greatly admire their working capacity. They have opened this field, which before them was quite hopeless.

On May 28, 1935, I answered.

> I have been interested in some physiological work on heparin recently; as a matter of fact, we have been administering some to human subjects. I hope that we will see you at the Physiological Congress in Russia this summer.

Up to the time of this letter there had been no published reference to the use of highly purified heparin in clinical cases but as Dr. Jorpes has written, the idea of using heparin to prevent the formation of thrombi was in the minds of all who came in close touch with the problem. Its realization merely depended on the availability of a satisfactory preparation of heparin. The clinical problem was attacked in Toronto and in Stockholm, as soon as pure heparin was obtainable. The studies by Crafoord[22] and later by other workers in Sweden, were proceeding at the same time as those of Dr. Gordon Murray[23] in the Toronto General Hospital. The results obtained clearly indicated that certain types of clinical thrombosis could be prevented by the treatment with purified heparin. These findings were made possible by the preparation of pure heparin from beef liver or lung. The word pure is used here to indicate a uniform preparation, of standard potency, and free from toxic components rather than in the true chemical sense.

Dr. Jorpes and his colleagues have made a very large number of fine contributions to the heparin field. The cellular origin of the anticoagulant, the chemistry, the mechanism of action, the clinical use in a great variety of conditions, and many other subjects have been illuminated by the work of this group, which

is well summarized by Dr. Jorpes[24, 25] in his monographs. I have had the pleasure of knowing a number of the Swedish "anticoagulationists" in addition to Dr. Jorpes. Dr. Per Hedenius and the late Dr. Hjalmar Holmgren have been particularly close friends.

Our present knowledge of the chemistry of heparin has been summarized by Dr. Arthur Charles[26] as follows: "Heparin is a complex polysaccharide. The carbohydrate moieties are glucuronic acid and glucosamine which are present in the molecular ratio of 1:1. The carbohydrate is highly sulphated. The amino group is not free and does not appear to be acetylated as in mucoitin or chondroitin sulphate. Evidence has been presented which indicates that the nitrogen is sulphated."

The availability of well standardized heparin not only made possible the clinical work but a very great deal of experimental study. Without this potent heparin the exchange transfusion experiments, carried out by Thalhimer, Solandt, and myself,[28] would not have been possible. The dramatic use of the artificial kidney by Kolff and Berk[29, 30] in Holland and by Dr. Gordon Murray in Toronto,[31, 32] also depended on purified heparin. I will not attempt to make a complete list of the advances which the availability of potent purified heparin has facilitated.

There will obviously not be time to follow in detail the many lines of interest which developed in the middle 1930's. Members of our own group were interested in the source of heparin and its appearance in blood in peptone and anaphylactic shock. The work on Witte's peptone goes back to the publication of Schmidt-Mülheim[33] in 1880, when it was shown that injection of the material in dogs produced shock and incoagulability of the blood. In 1909 Biedl and Kraus[34] found that the blood failed to clot in anaphylactic shock. Professor Howell[6] in 1925 and Quick[35] in 1936 had obtained anticoagulant preparations from dog's blood after injection of peptone. The subject was further advanced by Wilander[36] in 1939, who isolated heparin in amounts sufficient to explain the coagulation deficiency. Waters, Markowitz, and Jaques,[37] in our laboratory, showed in 1938, that the incoagulability of the blood, both in peptone shock and anaphylactic shock in dogs, was completely inhibited by protamine. The dramatic neutralization of the effect of heparin by protamine had been shown by Chargaff and Olson[38] in 1937. In 1940 Jaques and Waters[39, 40] isolated a barium salt of pure heparin from the blood of sensitized dogs given serum albumin.

Another point of interest in our laboratory was the enzymatic destruction of heparin by material prepared form rabbit's liver. This was carried out by Jaques[41] in 1940 and he suggested the name "heparinase" for this system. The use of silicone in preventing clotting was introduced by Jaques, Fidlar, Feldsted, and Macdonald[42] in my laboratory in 1946. This was a great improvement over vaseline or paraffin, which, of course, had been used ever since the work of Freund[43] in 1888 and of Bordet and Gengou[44] in 1901. A very great many experiments have been facilitated by the use of silicone coating of glass tubes, needles, and other apparatus.

The experimental work which D. Y. Solandt, Reginald Nassim, and I did[45] on the prevention of coronary thrombosis and intramural thrombosis in dogs by the administration of heparin, fascinated us until problems of military medicine diverted our attention in 1939. Dr. Solandt and I[46] described a method by which gradual occlusion of coronary arteries by thrombus formation may be produced in experimental animals. The thrombus formation and the resulting cardiac infarction were in a very large part prevented by the administration of adequate amounts of highly purified heparin. In discussing the possible clinical application of our findings I[47] wrote, in 1938, "If the clinical investigation of cardiac cases should be initiated, the necessity for studying very large numbers and of heparinizing only alternate cases is obvious."

In the investigation which Dr. Solandt and I made with Dr. Nassim, we evolved a method by which cardiac mural thrombi could be produced in animals. These thrombi were formed very rapidly and there was a very dramatic and extensive fall in blood platelets during this interval. The formation of the mural

thrombi could be completely prevented by the administration of adequate amounts of highly purified heparin. We[45] wrote at that time, in 1939, "Since over ten per cent of the deaths associated with coronary thrombosis in man are caused by embolic sequels of mural thrombus formation, a clinical trial of heparin is indicated."

There was an attempt, in Toronto, to apply some of these results, but no comprehensive investigation was found to be possible at that time. In 1948, Wright, Marple, and Beck[48] wrote, "The possibility of preventing the extension of coronary thromboses and the development of mural thrombi in the presence of myocardial infarction by the use of anticoagulants was suggested by Solandt, Nassim and Best in 1938 . . . Their observations were not applied to human beings on any significant scale because of the difficulties and the risk felt to be inherent in the use of heparin clinically."

When purified heparin became available in Toronto requests for this material for experimental and clinical use came from many parts of the world. One of the earliest was from Dr. Leo Mayer who wrote on December 21, 1938, "Dr. Irving Wright of the New York Post Graduate Hospital has suggested the advisability of using heparin in thi. case." The patient was Mr. Arthur Schulte. I remember sending heparin to Dr. I. S. Ravdin of Philadelphia who needed it for the postoperative treatment of a brilliant young doctor who had a saddle embolus at the bifurcation of his aorta. Many surgeons and physicians came to Toronto to discuss the clinical problems with Dr. Murray, or physiologic or chemical matters with our group. I remember many of these men vividly—Dr. Essex and Dr. Priestley of the Mayo Clinic and Dr. Lahey of Boston were among those who came from this country.

The interest in heparin continues to grow. Dr. Jay McLean was undoubtedly fascinated by the effect of heparin on the clearing of lipemic plasma, first demonstrated by Hahn,[49] and by the great volume of recent literature on the effects of the anticoagulant on fat mobilization.

Heparin has thus already removed many barriers to the free flow of knowledge but we are still in the early stages of appreciation of its physiologic and clinical significance.

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Heparin: A Mucopolysaccharide and an Active Antithrombotic Drug

By J. Erik Jorpes, M.D.

HEPARIN, like so many other biological substances, was discovered incidentally. William H. Howell, professor of physiology at Johns Hopkins University, Baltimore, was in 1916 trying to isolate a thromboplastin, an accelerator of the coagulation of the blood, from the phosphatide fraction of the liver and the heart. His co-worker, Jay McLean, found instead a substance, later called heparin, which retarded the coagulation of blood. Also unexpected was the finding made almost 20 years later in 1935 that heparin is a mucopolysaccharide esterified with sulfuric acid to a quite extraordinary degree.

The Chemical Nature of Heparin

The closest chemical neighbor of heparin, chondroitin sulfuric acid, was in the 1920's in spite of its interesting chemical composition still not easily accessible. It shared with the nucleic acids the property of being a macromolecular ester of a strong mineral acid, in this case sulfuric acid. In 1928, I succeeded in obtaining a protein-free chondroitin sulfuric acid having an almost theoretical content of ester sulfate by adsorbing the proteins on kaolin. This preparation was then used in our laboratory as a reference substance for checking the methods used for the quantitative analysis of uronic acids.

Among other natural products analyzed for uronic acids we also included in 1934 the heparin, claimed by Howell to give a positive color reaction for uronic acid. Heparin had been isolated in 1933 in a highly purified state by Charles and Scott of Toronto. In fact, the Tollens-Lefèvre technic showed a considerable content of uronic acid in heparin, a content which increased with increasing anticoagulant activity, making up almost 20 per cent of the dry substance of the purest heparin preparations.

The Tollens-Lefèvre technic is quite reliable and is easy to perform. The same could not be said about the methods applied for the biological assay of heparin. Cats were not so easy to get, and it was difficult to find the operating room and the assistants needed. An easier solution was then found. Series of test tubes containing a glass bead and serial dilutions of heparin solutions were filled early in the morning with fresh ox blood at the slaughter house, and readings of the coagulation times were made at intervals during the day. In 1 day several heparin samples of unknown strength could be compared with a standard heparin practically without any cost. This technic opened the field for further experimentation on a larger scale.

The purified heparin samples were found to contain large quantities of a hexosamine, which was later shown to be glucosamine, amounting to one mole of hexosamine per mole of uronic acid. At that time, 1933, Elson and Morgan had improved the Zuckerkandl-Klebermass method of 1931 for the quantitative analysis of hexosamines. We also believed that we had found acetic acid as a third component like that of the chondroitin sulfuric acid, but this assumption, based on faulty technic, soon proved to be erroneous.

The organic skeleton of heparin thus showed similarity to that of the chondroitin sulfuric acid. This acid, however, has no anticoagulant activity. The analysis of the ash, which amounted to not less than 25 to 40 per cent of the different preparations of the purified heparin, then gave the key to the problem. It was found to consist of sulfates exclusively. The sulfate was precipitable with barium chloride after the heparin was first hydrolyzed with mineral acid. This indicated an ester linkage

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of the sulfates similar to that in the chondroitin sulfuric acid. Now, when the sulfur analysis indicated a sulfate content of about 40 per cent in the purified heparin, 2½ times more than in chondroitin sulfuric acid, difficulties arose in convincing workers in this field that such compounds could exist in nature. It was an easy matter, however, to induce anticoagulant activity in ordinary polysaccharides by treating them with chlorosulfonic acid.

At almost the same time, 1938, however, Soda and Egami in Japan found in the visceral hump of a mollusca, *Charonia lampas*, a similar compound, a polysaccharide containing 15 per cent of sulfur as ester sulfate. Many years later, 1947 to 1950, Vasseur in Sweden showed that the mucous layer surrounding the sea urchin eggs contains plenty of polysaccharide polysulfuric esters with an ester sulfate content of about the same order as that of heparin. The organic skeleton of these compounds is built up of hexoses and methylpentoses, varying for different species.

It was thus evident that heparin belonged to a group of natural substances called mucopolysaccharides containing a hexosamine and a uronic acid, and that polysaccharides likewise highly esterified with sulfuric acid can be synthesized even by invertebrate animals. One detail, however, in the chemical structure of heparin is unique, the sulfamide or amidosulfuric acid group. In heparin, 1 sulfuric acid group is linked to the amino group of the glucosamine, as suggested by Masamune in Japan in 1940 and by Wolfrom in the U.S.A. in 1943 and finally demonstrated by our group in 1949.

It may not be quite out of place to point out that a neglected elementary analysis, in this case the sulfur analysis, evidently delayed the elucidation of the chemical nature of heparin, a by no means uncommon fatality. Liebig himself missed the phosphoric acid in his inosinic acid, the first nucleic acid described. Fifty years later it was shown to be a nucleotide. The sulfur content of taurine was likewise overlooked by Pelouze and Dumas in 1838. Also the sulfur of the thio-methyl pentose of the yeast was missed, and made the sugar difficult to identify until the sulfur was found by Zuzuki and Mori in 1926. Two oxygen atoms put into the place of 1 sulfur atom made the elementary analysis fit. Even the sulfur of vitamin B_1 escaped detection when the newly crystallized vitamin was analyzed by Jensen in 1926.

It must be pointed out however that Howell, although being a physiologist, did not miss the sulfur in the ash after igniting the heparin preparations, but he found it quite natural to speak about the ash as a contamination of the samples.

Heparin and the Mast Cells of Ehrlich

In 1936 the Stockholm group found that the heparin is produced by the mast cells of Ehrlich, a discovery which gave rise to an overwhelming literature dealing with these cells. Lison's finding of 1933 that the purple metachromatic staining of cartilage and mucous membranes given by toluidine blue is due to the ester sulfate group of chondroitin sulfuric acid caused me to apply the reaction to heparin. With heparin it was 100 times stronger than with the chondroitin sulfuric acid.

A stimulating observation was made when swine thoracic aorta was immersed for a short while in a 0.01 pro mille solution of toluidine blue. The most brilliant color in purple lila was developed on the inside of the aortic intima. We immediately anticipated that the heparin should form a superficial layer inside the aortic wall which with its ionized ester sulfate groups could exert some kind of repellent action. Unfortunately for the hypothesis, the metachromatic staining was due to the chondroitin sulfuric acid present in the intima.

The location of the heparin in the mast cells of Ehrlich was made by Hjalmar Holmgren, assistant at the Histology Department of our Institute. When we asked him to locate the heparin in the body by means of the metachromatic reaction, he could the next morning inform us that the mast cells of Ehrlich, a kind of cells quite foreign to us at the Chemistry Department, were carrying the heparin

in their granules. The quantitative analysis performed by Wilander also showed 10 times more heparin in the capsula Glissoni, the liver capsule, which is extremely rich in mast cells, than in the liver parenchyma itself. Since that time much, possibly too much, has been written about these cells and many more functions have been assigned to them than the order of Nature reasonably can have bestowed upon them.

Heparin as an Antithrombotic Drug

Clarence Crafoord, the well-known Swedish thoracic surgeon, had drawn attention to himself already as a very young physician through his numerous pulmonary embolectomies (between 20 and 30). What would be more natural in a case like his than to go to a biochemist and ask him to get out the heparin of Howell to be tried as a prophylactic against pulmonary embolism. This was in fact what Crafoord did in 1929. The only answer we could give him was unfortunately, "*Non possumus.*"

In 1935 we instead could approach him at the Sabbatsberg Hospital and ask him to try out our heparin preparations clinically. In the meantime Hedenius and Wilander had performed the first intravenous heparinization on themselves outside of the hospital. Their finding that 100 mg. or more of heparin are needed for heparinizing a human being for a few hours caused at first an almost desperate feeling. It seemed to be impossible to get sufficient material for a heparinization on a large scale. All the work on the chemistry of heparin had been performed on 6 Gm. We could not anticipate at that time that we in cooperation with a pharmaceutical house, Vitrum AB, Stockholm, within a few years should be able to produce 1 Kg. or more a week of the new substance.

Crafoord immediately started a series of experiments heparinizing patients postoperatively. Many an older colleague shook his head and expressed his dislike of such experiments, in which the patients were "made hemophiliacs" for a time. Crafoord, anyhow, fulfilled his intentions and treated 325 patients with heparin postoperatively. His colleague, Per Wetterdal, of the Gynecology Department of the same hospital, contributed another 231 cases and Leissner of the Maternity Clinic of the University of Lund heparinized 309 patients post partum. In total, about 800 cases were thus given heparin after operation or childbirth. A high frequency of thrombosis, at least 3 to 4 per cent and possibly still higher, was expected in Crafoord's series if untreated consisting only of patients over 35 to 40 years of age and with operations known to be followed by a relatively high percentage of thromboembolic complications. Practically no incident of that kind occurred. Although Wetterdal's and Leissner's series comprised only selected cases expected to give a high frequency of thromboembolism, no complications were observed during the first 10 to 15 days after operation or delivery. Among the 657 (325 + 140 + 192) cases receiving 250 mg. or more of heparin daily for 5 to 10 days no signs of thrombosis occurred.

Similar experiments were at the same time going on in Toronto, Canada. In order to demonstrate the usefulness of heparin in inhibiting thrombosis a series of animal experiments, initiated in 1932 in the Department of Surgery of the Toronto General Hospital, was performed in close conjunction with the chemical work on heparin at the Connaught Laboratories of the University of Toronto. These experiments were reported by Murray, Jaques, Perrett, and Best in 1936 and 1937. In 1938 Solandt and Best published their well-known paper about the dissolution of fresh thrombi in the coronary arteries of dogs by perfusing the vessels with a dilute heparin solution. Gordon Murray at the Toronto General Hospital contributed at first 260 cases and then a total of 400 cases treated prophylactically with heparin. He reported results equally as good as the Swedish group.

Thus the postoperative course of the more than 500 carefully controlled cases of Crafoord and of Wetterdal, supplemented by the 309 cases of Leissner and the 260 cases of Murray and MacKenzie, a total of 1,151 patients, seemed to prove that heparin, if rou-

tinely used over a sufficient length of time, gives an almost complete protection against thromboembolic complications after surgical operations and childbirth.

Anticoagulant Therapy in Thrombosis

As a result of the lively interest in heparin following Crafoord's first publication in the spring of 1937 on prophylactic heparin treatment in man and our discovery of the connection between heparin and the mast cells of the same year, a physician in Stockholm, Holmin, later in the year tried the new remedy in a case of fresh acute thrombosis in the central retinal vein in a young person. Well aware of the hopeless prognosis, he gave a tentative dose of pure heparin intravenously 3 to 4 times daily over a period of 10 days beginning on the third day of the illness.

Ploman describes the course of this case as quite unusual, for the patient regained a visual acuity of 0.9 in 9 days. In a second case, described by Boström and William-Olsson, where the lesion was 1 month old, visual acuity rose from 0.1 to 0.4 in 5 days and later to 0.6. The unusual course of these 2 consecutive cases made these ophthalmologists inclined to ascribe the result to the treatment with heparin.

In the same year Magnusson (1938) used heparin successfully in a case of thrombosis of the posterior inferior cerebellar artery, Wallenberg's syndrome, a disease in which a regression is unusual. In 1938, Murray and Best reported 28 cases of spontaneous thrombophlebitis and 7 cases of pulmonary embolism treated with heparin. All the cases of embolism showed rapid clinical improvement, and the 28 cases of spontaneous thrombophlebitis showed no evidence of embolism, and the clinical signs and symptoms, pain, swelling, tenderness and fever, appeared to show more rapid improvement than in a control group.

In his second paper Crafoord (1939) stated that he had given heparin to 20 patients with manifest, thromboembolic complications. In some of these both the general and local symptoms receded strikingly rapidly.

In Sweden, Magnusson (1940) administered heparin to a woman with severe pulmonary embolism and thrombosis in both legs, complicating a postpartum scarlatina. The temperature became normal in a few days and the patient, who had been ill for 6 weeks with repeated thromboembolic recurrences and was very emaciated, recovered.

After these most dramatic and very convincing preliminary experiences with heparin discussion of the anticoagulant therapy was broadened and taken up on a larger scale in different parts of the world. It was quite evident that there could be no question about a general prophylactic heparinization. Early rising after operations and childbirth makes such a measure superfluous except in some cases with a pronounced tendency to thrombosis. Then Karl Paul Link's work, leading to the discovery and synthesis of Dicumarol, broadened the field in a highly desirable way by making a prolonged anticoagulant therapy possible. The easily accessible oral drug also proved a prerequisite for long-term prophylactic treatment.

It may be added here that active movements and early rising from the bed are now generally prescribed and strictly applied in most countries. The question then arises to what extent the beneficial effects of the anticoagulant therapy observed are due to the anticoagulants or to the movement therapy. In fact the most critical observers in Denmark, the country of Hans Christian Andersen, have spoken about the Emperor's New Clothes in thinking of the advocates of the anticoagulant therapy, a very sound criticism indeed. Without active movements and early rising from the bed the effect of the anticoagulant treatment would certainly not have been so good.

It is in fact impossible to evaluate these experiences correctly. The fact remains, however, that thrombosis can be prevented through prophylactic heparinization. As to anticoagulant therapy in thrombosis, it must also be kept in mind that prior to this therapy thrombosis of the veins of the legs used to be so painful and the legs so swollen that there could be no thought of active movements and early rising. Anybody treating a severe leg

thrombosis or a pulmonary embolism with heparin will soon be impressed by the amelioration of the pain and of the feeling of oppression, and by the disappearance of the swelling of the leg. It would also have been deplorable if the medical profession had been unable to detect the value of the movement therapy without the stimulant of the new anticoagulant therapy. Until the most recent years thromboembolic patients were kept in bed for 6 to 8 weeks.

Under the influence of this discussion a gynecologist at one of our university clinics decided to treat a series of cases of acute thrombosis without heparin. The first patient was sent home and instructed to move around as much as possible. A few days later she came back with a florid phlegmasia alba dolens. His series comprised only this case.

In the beginning of the 1940's the large-scale clinical experiments with the anticoagulant therapy had begun in Sweden (Hellsten, Bauer, Zilliacus), in the U.S.A. (Allen, E. V. and Barker, N. W., Wright, I. and co-workers, de Takats, G.), and in Switzerland (Merz, R. W.). Heparin and Dicumarol thereby left their cradle, the laboratories of physiologic and organic chemistry. They both proved valuable enough to keep their position in a world where new therapeutic products flourish and disappear in a continuous stream. An almost immense literature already tells their story.

In speaking about the cradle of heparin it is not out of place to mention that the writer had the pleasure of being able to inform William H. Howell of Johns Hopkins University during his last years about the successful progress of the anticoagulant therapy in this part of the world. Needless to say, these reports were welcome. They told him that something of permanent value will remain as a result of his contributions to physiology. They might also to some extent have enlightened those dark days during the war, as that of April 11, 1942, when he wrote, "When this killing and shooting is all over I fear that this world will not be such a pleasant place to live in as it was in my youth—and I shall have no great regrets in leaving it, although I would dearly love to know what steps will be taken to assure a permanent peace."

The Development and Use of the Prothrombin Tests

By ARMAND J. QUICK, M.D., PH.D.

PROLOGUE

Take from the altar of the past,
the fire—not the ashes.
Jean Jaures

At the end of the last century, the fire on the altar of coagulation was burning briskly, for it had been well fed with the fuel of ideas and experimental findings by such workers as Buchanan, Schmidt, Hammarsten, Pekelharing, Arthus and Pagès, and Morawitz. After 1900 the flames began to die down, partly because fewer new ideas were forthcoming and partly because the fire was smothered by confused theories and poorly executed experimental work. Such simple instruments of precision as the pipet and the stopwatch had not generally found their way into the physiologic and clinical laboratory; the workers were content to measure volume in drops and to record reaction times in minutes and hours instead of seconds. Fortunately, there remained in the embers much that could be rekindled. In 1890 Arthus and Pagès[1] had discovered that the blood became incoagulable when sodium oxalate was added and that the addition of calcium restored clotting. Twenty years later Addis[2] employed the principle of timing the clotting of recalcified plasma, and shortly thereafter Howell[3] standardized the method and demonstrated its usefulness. He believed that the test was a measure of prothrombin. Since the clotting time of recalcified plasma is prolonged in hemophilia, he concluded that a prothrombin defect accounted for the abnormal coagulation in this disease. Later, however, he and Cekada[4] obtained evidence that the prothrombin was normal in hemophilia. This conflict made the interpretation of the test difficult and resulted in considerable confusion because the procedure continued to be called a prothrombin test. In 1929 Bancroft, Kugelmass, and Stanley-Brown[5] employed the test to study thrombosis and certain bleeding states. They observed a delayed clotting in hemophilia and also in a number of cases of jaundice. Nygaard[6] at the Mayo Clinic confirmed the delayed clotting of recalcified plasma in jaundiced patients. He concluded that the coagulability was decreased, but he refrained from offering any explicit explanation. This is understandable when one recalls that at this time the classical theory, which eventually furnished a satisfactory and practical answer, had won little recognition in America.

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ACT I, SCENE I

In 1932 the stage was set for a new attack on the problem of the coagulation of the blood and on the hemorrhagic diseases. One scene was at the State University of Iowa in the laboratory of the Pathology Department, the other in a little corner in the laboratory of the Fifth Avenue Hospital of New York. Since I played an active role in the latter scene, it is easiest to tell the story in the first person.

As already mentioned, Dr. Bancroft and Dr. Stanley-Brown had begun a study on the coagulation of the blood with the aim of attacking the problem of postoperative thrombosis. They had obtained a grant of money from Mrs. Blossom, of Cleveland, for this investigation which enabled them to pay a full-time fellow. I learned of this through my teacher and friend, the late Dr. Joshua Sweet, and when I was offered the opportunity to work with them, I accepted with some hesitation and trepidation for I knew nothing about blood coagulation.

From Mrs. Charlotte Breitung, the technician, I learned the technic of the clotting time of recalcified plasma. As the studies progressed, I confirmed what Dr. Bancroft and his associates had already reported,

namely, the prolonged clotting time in hemophilia and in certain patients with obstructive jaundice. Difficulty was encountered, however, when I attempted to correlate a thrombotic tendency with a shortening of the clotting time of recalcified plasma. It became obvious that the test had to be rigidly standardized. To do this I had to know more about the theory of blood clotting and also to gain additional practical experience.

In meeting the first requirement, I had the good fortune to have the Academy of Medicine with its excellent library within walking distance. Evening after evening I struggled to find my way through the maze of conflicting theories. To say that the current literature of that period was bewildering is to understate the facts. A few investigators denied even the existence of prothrombin. Fortunately, however, Wöhlisch[7] had written an excellent review which summarized the earlier literature on blood clotting. For the first time, I became familiar with the classical theory of Morawitz and of Fuld and Spiro. Gradually, the confusion cleared as I became converted to the creed of the classical theory. The bewilderment encountered in reviewing the literature was no worse than my own groping in the laboratory. Dr. Stanley-Brown, Mrs. Breitung, and I began to study various problems such as the effect of splenectomy on the clotting time, the changes in the blood caused by injection of heparin, and the relation of prothrombin to the end piece of complement. While we made a few interesting observations, little real progress was forthcoming. The clotting time of recalcified plasma continued to interest me and after I became familiar with the classical theory, the well-known equation

Thromboplastin + Ca + prothrombin = thrombin

made its appearance in my notebook. As one trained in fundamental chemistry, I noted the 3 variables in the equation and recognized that only calcium was controlled in the clotting time of recalcified plasma. The need to find a suitable thromboplastin reagent was my first concern. The only materials that were readily available were the tissues of small laboratory animals. It was indeed lucky that the first material I tested was rabbit lung which I found had a relatively high thromboplastin activity.

On January 6, 1934, I observed the first abnormally prolonged clotting time with the test. It was on a plasma from a jaundiced patient. Two days later I obtained similar results on a second jaundiced plasma. I did not attach too much significance to these findings, since the results were often erratic; nevertheless, I made this notation on January 30, "I am still interested in a direct prothrombin test by adding lung extract directly to plasma." I continued to have difficulty with lung extract as a thromboplastin reagent and I soon found that rabbit brain gave more constant results. To preserve the material I spread it on a glass plate as a thin paste and air dried it; from this the extract was made.

Gradually, I began to recognize the possible importance of the new test and was anxious to apply it clinically. Dr. Bancroft arranged with various hospitals (Mount Sinai, Lennox Hill, Doctors', Presbyterian, and St. Luke's) to allow me to collect blood from their jaundiced patients. In a short time through excellent cooperation we had a series of cases of obstructive jaundice with definitely prolonged clotting times as measured by the new test. We also had the opportunity to study a number of hemophilic patients, and found that their clotting times were consistently normal. These results with a description of this new test were presented in a paper which we submitted to the American Journal of Physiology in the early summer of 1934. After 2 months it was returned with the comment that 3 editors had agreed that the paper was "not acceptable." Ten years later the American Medical Association awarded a gold medal for our exhibit that was based essentially on the material contained in that article.

Because of the uncertainty of further financial support of the grant, I left New York in November 1934 to enter private practice in Milwaukee. Thus, the first phase of the development of the 1-stage prothrombin time

was completed. Sufficient evidence had been gathered to show that the test had possible clinical usefulness. A report[8] of the work was published in April 1935. With this, the curtain dropped and my pleasant and stimulating association with Dr. Bancroft and Dr. Stanley-Brown was terminated.

Act I, Scene 2

The second scene was laid at the State University of Iowa. Dr. Harry Smith who, as a medical student, had worked on plasma proteins under the guidance of Dr. George Whipple became interested in fibrinogen. Later, in collaboration with Dr. T. B. Jones, he studied the fibrinogen level of the blood after hepatectomy. This brought him into the orbit of blood clotting. With his associates Brinkhous and Warner, he organized an extensive research program. One of their first important contributions did much to reestablish faith in the classical theory. Wooldridge,[9] later Nolf,[10] and in this country, Mills,[11] had built an elaborate theory in which tissue coagulins independent of thrombin occupied a central position; in fact, thrombin was regarded as a by-product. When Smith and his co-workers[12] showed that an extract of lung carefully freed of blood did not clot fibrinogen, it became clear that tissue coagulins were merely mixtures of prothrombin and thromboplastin, and that thrombin was the sole agent that converted fibrinogen to fibrin.

As a sequela to these studies, Smith and his associates[13] developed a quantitative method for prothrombin. Their method likewise was based on the classical theory and they, too, added an excess of a tissue extract to convert prothrombin to thrombin. Instead of measuring the evolution of thrombin directly, however, they devised a procedure in which the conditions were such that the total amount of thrombin formed was measured. This required, first, defibrination and then dilution of the plasma before adding a mixture of lung extract, calcium, acacia, and buffer to generate thrombin. The latter was determined by the speed with which it clotted a standardized solution of fibrinogen. To distinguish the 2 methods, mine was called the 1-stage test while that of Smith, the 2-stage, though actually this was a multistage procedure. The 2 methods, developed independently and almost simultaneously, agreed remarkably well as measures of the hypoprothrombin in vitamin K deficiency, as well as in other states. Differences, however, were encountered and only after many years did it become apparent that the methods did not always measure the same clotting factors and that neither test was an infallible determinant of prothrombin. In the hands of Smith, Brinkhous, and Warner, the 2-stage method supplied much valuable information on prothrombin. One of the casualties of World War II was the disruption of the Iowa team. Eventually, Dr. Seegers, who had joined the group in 1937, became the chief custodian of the 2-stage method and its citadel was moved across Lake Michigan to Wayne University, at Detroit.

Act II

The drama of the 1-stage method shifted to a new scene—a laboratory in the Department of Biochemistry at Marquette University School of Medicine put at my disposal by Dr. Joseph Bock. Since my medical practice did not encroach much upon my time, I was again able to resume active work on tissue thromboplastin. I had noted in my earlier study that the common lipid solvents with the exception of acetone impaired the thromboplastin activity of the material. This clue enabled me to develop a method[14] for the dehydration of rabbit brain with acetone. In this manner a product was obtained which not only had a high and remarkably constant activity but also possessed stability. With this agent a prothrombin time of 12 seconds on human plasma has been consistently obtained in our laboratory for the past 20 years and, interestingly, preparations made in 1938 and kept at room temperature in evacuated ampules have retained full activity until now. Having achieved the goal of producing a thromboplastin reagent of constant activity, it was possible to construct a curve relating the prothrombin time to prothrombin activity.[15] The well-

known hyperbolic curve could be expressed by the equation

$$\text{Prothrombin activity} = \frac{K}{p.t. - a}$$

With a prothrombin time (*p.t.*) of 12 seconds, the values of the constants K and a were established as 330 and 8.7, respectively.

While perfecting technically the 1-stage procedure, I was on the alert to find opportunities for applying the test. In this quest, June 9, 1936, was indeed a memorable day. I took a drive to Madison and visited my former teacher, Professor E. B. Hart, who told me of the interesting work Almquist[16] was doing on a new dietary deficiency disease that gave rise to a bleeding tendency and also of the studies in their own department on a bleeding condition caused by spoiled sweet clover hay. Later that day I learned more about this interesting disease from Dr. Link, who was working on the isolation of the toxic principle of this hay, and from Dr. W. K. Smith, who was interested in the genetic aspects of sweet clover. In the course of our conversation, I acquainted them with my prothrombin method and voiced the wish to apply the test to this bleeding condition. Dr. Smith offered to send me a bag of this toxic hay. None of us, I am sure, realized the far-reaching consequences that resulted from this mutual exchange of ideas and materials.

Immediately on my return to Milwaukee, I prepared the special diet of Almquist and began feeding it to newly hatched chicks. Soon after the bag of spoiled sweet clover hay arrived, I started feeding it to several rabbits. Much to my delight a striking increase in the prothrombin time occurred in the chicks and also in the rabbits. In both a bleeding tendency manifested itself when the prothrombin time became moderately prolonged. This was probably the first time that the results of a clotting test were quantitatively correlated with a bleeding tendency. I found that the addition of as little as 1 per cent of alfalfa meal to the Almquist diet greatly shortened the chicks' prothrombin time and cured their bleeding. I further noted that when the toxic hay was mixed with alfalfa meal, it no longer caused hypoprothrombinemia. These findings helped to explain the hypoprothrombinemia which we had observed in jaundiced patients, namely, that a vitamin K deficiency, probably caused by faulty absorption due to the absence of bile in the intestines, resulted in an inadequate production of prothrombin.

The results of these studies as well as the important contributions of Smith and his coworkers established the validity of the classical theory more firmly than ever. For a brief period there was general agreement as to the basic clotting reaction, but this halcyon interlude was of short duration. A new era of turbulence began which was at least in part set off by a simple experiment done with the 1-stage method, the results of which I published in 1943.[17] On adding stored human plasma that had a prothrombin time of 40 seconds to an equal volume of plasma from a dog given Dicumarol, which likewise had a prothrombin time over 40 seconds, I obtained a mixture that had a prothrombin time of 10 seconds. This mutual corrective action clearly indicated that the clotting factor lost during storage was different from the one decreased by Dicumarol and that what had been called prothrombin was actually an activity depending on at least two factors.[18] This discovery of a new factor made the classical theory no longer tenable. Its foundation had begun to be undermined, and the method that was largely responsible was the simple 1-stage prothrombin time that owed its very existence to this theory.

Epilogue

With the passing of the classical theory, a notable period in the study of the clotting of blood came to an end and an exciting new era had its beginning. Interestingly, many of the new methods which are at present extensively employed, such as the prothrombin consumption time, the partial thromboplastin test, and the thromboplastin generation test are direct outgrowths of the simple 1-stage prothrombin time and are based on the same fundamental principle—measurement of the speed of thrombin production. The principle of the

2-stage method likewise continues to serve as an important tool for research in coagulation. Gradually, it is being recognized that the 1- and 2-stage procedures often complement each other. Both continue to supply fuel for the fire that should light the way for a better understanding of the complex coagulation mechanism.

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The Discovery of Dicumarol and Its Sequels

By KARL PAUL LINK, PH.D.

THE STORY of Dicumarol* has been told several times by me in the past 17 years, and often by others. Like any good story it need not be told in exactly the same manner each time. In Wisconsin it has become a kind of legend. I shall consider only the high water marks of certain chapters.

Fortunately the basic scientific facts on the discovery and development have already been thoroughly recorded[1-6] so that little new information on Dicumarol and its sequels needs to be revealed here. However, when I do introduce new material it will be restricted to that which is documented or sustainable via memoranda or letters.

The story begins some 36 years ago on the prairies of North Dakota and in Alberta, Canada. In the 1920's a new malady of cattle involving fatal bleeding showed up almost simultaneously in these areas. The veterinarians, Schofield and Roderick, were forced to conclude that the cause of the disease was neither a pathogenic organism nor a nutritional deficiency. The origin of the new malady was traced to stacks of sweet clover hay mysteriously gone bad. Hence the disease became known in veterinary practice as "sweet clover disease" and it was found that it was caused *only* by improperly cured hay made from the common varieties of sweet clover. When first observed this disease was in a sense without parallel in animal pathology or human medicine. When cattle or sheep ate the spoiled hay the disease slowly became manifest by a progressive diminution in the clotting power of the blood (about 15 days) and resultant internal hemorrhage which usually became fatal in about 30 to 50 days.

It was recognized by Schofield and Roderick that the disease was reversible. It could be controlled in cattle by the withdrawal of the spoiled hay from the diet and by transfusion of blood freshly drawn from normal cattle, provided the hemorrhagic extravasation had not proceeded too far. Indeed, they showed that even in desperate cases, recovery could be hopefully anticipated after transfusion and change in diet (good hay).

In a comprehensive and thorough study of the pathology and physiology of the disease Roderick in 1931 emphasized that the delayed or abolished coagulability of the blood was due to a "prothrombin" deficit. Indeed he showed that the severity of the hemorrhagic condition paralleled the reduction in "prothrombin content or activity." He did this by using the technic developed by that great American pioneer of blood coagulation, the late Professor W. H. Howell. Solutions of what was then called "prothrombin" prepared by precipitation of normal bovine plasma with Howell's acetone method when added to the "sweet clover blood" promoted coagulation. In contrast, preparations of "prothrombin" made in a parallel manner from "sweet clover blood" did not produce coagulation. The other constituents for the maintenance of normal coagulability known at that time (fibrinogen, calcium, platelets, and inhibitory substance) appeared to be unaffected.

I first learned about the hemorrhagic sweet clover disease of cattle in December 1932 through the late Ross A. Gortner, who then

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Given February 25, 1958 at the New York Academy of Medicine under the auspices of the Section of Medicine and the New York Heart Association, on the programme, "The Historical and Physiological Aspects of Anticoagulants."

*Dicumarol is the trademark for 3,3'-methylenebis-(4-hydroxycoumarin). The anticoagulant was made available in 1940 and 1941 for clinical use by the cooperative efforts of the Wisconsin Alumni Research Foundation, Madison, Wis., the Abbott Laboratories, North Chicago, Ill., Eli Lilly and Company, Indianapolis, Ind., and E. R. Squibb and Company, New Brunswick, N. J. The official U.S.P. name is bishydroxycoumarin.

headed the Biochemistry Department of the University of Minnesota. He had offered me a post and I had come to St. Paul to consider it. Since the "sweet clover disease" was also a problem in Minnesota it was one of the projects open for study if I chose to accept. It was Gortner who supplied me with the original publications of Roderick. Some attempts had been made in Gortner's department to extract the hemorrhagic agent but they, like those of Roderick and others, had failed.

Curiously, the "official start of *our* work in January 1933 in cooperation with Professor R. A. Brink and W. K. Smith of our Genetics department was on a different aspect of the sweet clover problem. They sought to develop a strain of sweet clover suitable for Wisconsin climatic conditions low in, or free from, coumarin. Though coumarin smells sweet (the characteristic smell of new mown hay is due to its presence) it tastes bitter, and it was known that the bitter taste of green sweet clover plants, Melilotus alba and M. officianalis, paralleled the total coumarin content. In actual practice it was observable that cattle (or rabbits) would eat the less bitter plants first.

Tragedy out on the Farm

Quite apart from the "official" start concerned primarily with the palatability question my laboratory had a direct catalytic hit from agricultural practice.

Indeed on a Saturday afternoon in February 1933 following the first conferences with Brink, while a blizzard was howling and the mercury was hovering near zero, a farmer from the vicinity of Deer Park, Wisconsin, some 190 miles from Madison appeared with what the late Professor A. J. Carlson might have called "the evidence." Curiously the farmer's name was Ed Carlson. The hemorrhagic sweet clover disease of cattle was rampant on his farm. He had fed sweet clover hay for years previously without encountering any difficulties and he doubted the veterinarian's diagnosis. Accordingly he was advised to go to the Agricultural Experiment Station authorities to get the facts. The office of the State Veterinarian had closed and pure chance had brought him to the Biochemistry Building.

Farmer Carlson's multiple evidence was a dead heifer, a milk can containing blood completely destitute of clotting capacity, and about 100 pounds of spoiled sweet clover—the only hay he had to feed his cattle.

His account of the over-all course of the disease coincided perfectly with the classical "sweet clover poisoning" picture. Late in December he had lost 2 young heifers. In January 1 of his favorite old cows had developed a massive hematoma on a thigh and following a skin puncture fatal bleeding set in rapidly. Finally 2 young cows had died on Friday and the bull was oozing blood from the nose. So he took off for Madison in a blizzard.

I immediately had to tell farmer Carlson that we could do no more at this time than to recommend the teachings of Roderick and Schofield. He had to stop feeding *that* hay, and possibly transfuse those desperately sick cattle, if he wanted to save them. Eventually it might become possible to make some usable recommendations to avoid such disasters, but not now.

I can still see him take off for home about 4:00 p.m. Those 190 miles of drifted roads between our laboratory and his barn must have appeared to him like a treacherous and somber ocean.

I cannot take the time to tell all the details of this slice of the Dicumarol story, but I can assure you its impact on me was immense. I will relate a part of it exactly as I did in my first lecture on Dicumarol given at the Mayo Clinic on March 12, 1942.

When farmer Carlson came to see us, my senior student and old man Friday was Eugen Wilhelm Schoeffel, a volatile Schwabian who came to the U.S. in 1926 with a diploma in Agricultural Chemistry. After serving a 2-year apprenticeship in the Chicago Stock Yards he began to study with me in 1929. Schoeffel is interesting, energetic, and loyal. He was then and still is, somewhat of a mystic and inclined in ordinary conversation to quote freely from Goethe's Faust, Shakespeare, and the Bible, as well as other primary sources. In 1933 his spoken English was not only strongly guttural, but also very earthy, punctuated frequently with Schwabian German.

After farmer Carlson left, Schoeffel stormed back and forth in the laboratory shouting, 'Vat da Hell, a farmer shtruggles nearly 200 miles in dis Sau-wetter, driven by a shpectre and den has to go home vit promises dat might come true in five, ten, fifteen years, maybe never. Who knows? 'Get some good hay—transfuse.' Ach!! Gott, how can you do dat ven you haf no money?'' he snarled.

He dipped his hands into the milk can repeatedly and while rubbing them muttered, 'Dere's no clot in dat blook! BLUT, BLUT VERFLUCHTES BLUT. 'Die Menschen dauern mich in ihren Jammertagen.' '' (Faust Prolog., line 297) and then, ''Vat vill he find ven he gets home? Sicker cows. And ven he and his good voman go to church tomorrow and pray and pray and pray, vat vill dey haf on Monday? MORE DEAD COWS!! He has no udder hay to feed—he can't buy any. And if he loses de bull he loses his seed. Mein Gott!! Mein Gott!! Vy didn't ve anti-shi-pate dis? Ya, ve should haf anti-shi-pated dis.''

We took the blood and hay and played about with them until about 7:00 p.m. when I headed for home. As I left the laboratory, Schoeffel grabbed me by the shoulders, looked me squarely in the face and said, ''Before you go let me tell you something. Der is a deshtiny dat shapes our ends, it shapes our ends I tell you! I vill clean up and gif you a document on Monday morning.''

Development of the Bioassay

Two fundamental issues confronted us. First there were no *chemical* criteria available to establish the presence of the hemorrhagic agent. Therefore, a *bioassay* involving a small experimental animal (rabbits)) offered the only practical means of appraising the anticoagulant activity of test hays and extracts prepared therefrom.

It was clear from the pioneer papers of Roderick that the sweet clover disease *was completely reversible.* The eating of spoiled hay, even over long periods, caused no permanent functional change, no demonstrable morphologic change, and no detectable pathologic change of the liver, the assumed primary site of prothrombin synthesis. Nevertheless, the immediate prospects of developing a reliable and simple bioassay were not bright; indeed they were dark, ''dark like the inside of a cow.'' We had not had previous experience with that complex problem—blood coagulation.

Schoeffel and Roberts first showed that the Howell method for estimating prothrombin activity did not have the precision required. Smith and Roberts showed that the whole blood coagulation time was too variable, and that the Quick 1-stage method using whole plasma left much to be desired. Smith also showed that there was a wide variation in the response of individual rabbits to the standard dose of 50 Gm. of the spoiled hay. So Campbell and Smith bred and reared a susceptible rabbit colony specifically for the assay.

At that time, 1935-1938, a bloody and amusing polemic raged among the coagulation specialists on how to estimate ''prothrombin concentration or activity''—whether it should be done by the 1-stage method of Quick* or the 2-stage method of H. P. Smith and coworkers.[1-3, 8] We tried to keep out of that brawl. In 1938 Campbell finally got over the chief obstacles. He adapted the Quick 1-stage method to our conditions, primarily by relying on the clottability of diluted plasma within the concentration range 12.5 to 8.34 per cent. He eliminated some of the inherent daily variations by fasting the assay rabbit 24 to 36 hours before feeding any preparation under test, by making the plasma clottability tests promptly after drawing the blood, and by comparing the test plasma against the normal plasma of each rabbit.

Through the use of individually standardized rabbits (the standard response being that

*The intricacies of the blood coagulation phenomenon are outside the scope of this discourse. Suffice it to state that it is now accepted by most ''coagulationists'' that a prolonged Quick 1-stage ''prothrombin time'' (when the fibrinogen is normal) induced by Dicumarol and the like is a primary deficiency in factor VII and prothrombin. See British Medical Bulletin, vol. II, no. 1, Blood Coagulation and Thrombosis, Medical Department, The British Council, London, November (1955), and the lectures by Owren P. A. on Coagulation of Blood, etc., Northwest Medicine, January, pp. 31-39, February, pp. 159-166, and March, pp. 298-307, 1957.

induced by the anticoagulant in 50 Gm. of spoiled hay) and by having the assay on a strictly differential basis the ever present problem of biologic variation was greatly reduced.

Some side observations were made by Campbell on the plasma of rabbits fed the spoiled hay or fractions thereof that were later reported by others. A plasma factor beyond that needed by the classical blood coagulation expression of Morawitz-Field and Spero was hinted at in one of Campbell's reports. But these hares were not hunted. Our goal was to make real a substance that abolished the clottability of cattle blood in agricultural practice. To use the vernacular, the bioassay using the 1-stage plasma clottability was altered so that "it worked," and few of the valuable assay rabbits were lost in the process. One of them known as Bess Campbell was used for about 200 individual assays, over a period of 5 years.

Isolation, Crystallization, Identification, and Synthesis of Dicumarol

Between that fateful Saturday in February 1933 and June 1939 a long and arduous trail was followed by Smith, Roberts, and especially Campbell, to lay the anticoagulant out on the bench. I would like to detail some of the chemical extraction, separation, and isolation problems that the spoiled sweet clover hay presented. This hay was indeed a kind of biochemical grab-bag and yielded many inactive products, some new, most of them old. But suffice it to state that many a seething and simmering hope did not become reality. At times the hemorrhagic agent appeared to hover before us like thistle down only to elude us like the will-o-the-wisp. At one time it was thought to be a porphyrin-like substance, a pheophytin resulting from the degradation of the chlorophyll in the spoiling process.

Finally in the dimness of dawn on June 28, 1939, after working all night, Campbell saw on a microscope slide what turned out to be crystalline Dicumarol. Two hours later he had collected about 6.0 mg. of it.

When I reached the laboratory that morning Campbell was asleep on the laboratory couch; the door to the room was guarded by one Chet Boyles, a soldier of fortune on the W.P.A. relief roles, who assisted Campbell with the bioassays. Boyles was an excellent handler of animals for he had served 2 years as helper to a veterinarian before he came to us.

As I walked into the room, Boyles was taking a nip from the contents of a bottle whose bottom layer consisted of carpet tacks, the upper layer of 95 per cent ethanol. Without the flicker of an eyelash Boyles said to me, "I'm celebrating, Doc. Campy has hit the jack-pot." (As though I didn't know that he had been hitting that bottle for months.)

But Boyles' surmise was correct this time. Campbell did have Dicumarol and the first bioassay to establish its anticoagulant potency was already in process!

Campbell avoided me for 2 days—until the results of the assay were available—and then he came in to report.

There is a bed-rock of matter-of-fact common sense in Campbell's makeup. He was not inclined to show his emotions, but it was apparent that he was secretly as happy as a boy who had just caught his first big fish. He passed the vial to me and said, "This is H. A.!" (H. A. was the laboratory code for hemorrhagic agent.) I did not disclose that Boyles had given me the tip-off. I told Campbell that I knew a couple of lines of German poetry that fitted the occasion, and I recited to him,

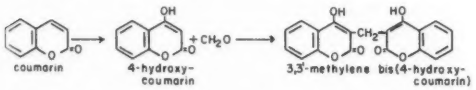
"So halt'ich's endlich denn in meinem Händen
Und nenn' es in gwissen Sinne mein."

We sent a short wire to Schoeffel, who was then in the control laboratory of the American Medical Association in Chicago. He responded at once with a 200-word reply wherein he expressed his *complete* confidence in Nature, Fate, and us.

Mass isolation was started at once, and a stock of about 1,800 mg. of the crystalline anticoagulant was accumulated (Stahmann).

The problem of determining its structure fell to the sensitive, brilliant, and deft C. F. Huebner, who with some assistance from his lively imagination made the correct structural diagnosis as 3, 3′-methylenebis (4-hydroxycoumarin). He set the sights for the synthesis, which was achieved on April Fool's day, 1940. The synthetic and the natural product were shown to be chemically identical. Subsequently, Overman and Sullivan, through carefully conducted tests on the rabbit, rat, guinea pig, mouse, and dog, hall-marked the natural and synthetic products as biological equals.

The determination of the structure of the anticoagulant as a 3-substituted derivative of 4-hydroxycoumarin makes it appear that both of the undesirable aspects of the common sweet clovers—their unpalatability (bitterness) in the green state and the tendency of the hays to cause hemorrhage when improperly cured—have a common basis in the coumarin molecule. The biological synthesis during spoilage can be rationalized as an oxidation of coumarin to 4-hydroxycoumarin which upon coupling with formaldehyde leads to Dicumarol.



Physiologic Action of Dicumarol

After synthetic Dicumarol became available in quantity the essentials of its physiologic action were quickly established. It was shown that there is a lag in response, a variation in the intensity and duration of the hypoprothrombinemia (plasma prothrombin clotting time), depending on the size of the dose. In each species tested a certain single dose level gives the most efficient response. Below this level the efficiency of action is decreased by a threshold effect and at high levels by incomplete absorption of the drug.

Due to the latent or lag period of 12 to 24 hours before the drug's action becomes apparent, there is a cumulative effect following repeated administration. Thus it was anticipated that in clinical practice this action will vary with the individual and because of this variation optimal therapeutic effects without hemorrhage would be obtained only when the dosage is individualized.

A brief summary[1-3] of the details follows:

1. There is a wide species difference in the response induced in the rabbit, rat, guinea pig, mouse, dog, cat, and chicken, and this varies with the age and sensitivity of each individual. Broadly speaking, the rat and mouse are the most sensitive, the cat and dog intermediate, and the rabbit, the cow, and the chicken the least sensitive.

2. The vitamin K and C levels in the diet affect not only the intensity but also the duration of the anticoagulant action. I propose to elaborate on this later.

3. The nutritional status of the animal affects the anticoagulant response—fasting generally enhances it in all species.

4. Any pre-existing hypoprothrombinemia like that inducible by the salicylates (aspirin), the sulfa drugs, or mild chloroform anesthesia *augmented* the response.

5. The hepatic and renal function influences both the intensity and duration of the response.

6. The presence of drugs that affect the total functioning capacity of the liver, like the methylxanthines (theophyllin) and the digitalis drugs, have a mild but definitely detectable counter action.

7. Pregnant or lactating females show a slight resistance to the drug's anticoagulant action.

These observations did not exhaust the conditions that can influence Dicumarol's action but they cover the essential points. Finally, it should be added that in Dr. Best's department at Toronto, Dale and Jaques first[9] and later Meyer and co-workers[10] at Wisconsin General Hospital, and others[11-13] were able to show that a primary relationship exists between thrombus formation and the clotting mechanism of the blood. These studies established for the first time that an effective reduction of extravascular and intravascular thrombus formation parallels the diminished hypocoagulability induced by Dicumarol. It

was also shown by Spooner and Meyer[14] that, when Dicumarol is given to dogs in safely usable therapeutic doses, it definitely decreases platelet adhesiveness; at the same time Quick showed that it also reduced platelet agglutinability.[15] Thus the clinical use of the anticoagulant as a prophylactic agent for (against) thrombosis rested on a sound experimental basis.

Breaking the Bonds of the Usual Pattern of Thought

When we turned Dicumarol over to the clinicians in the years 1940 to 1942, one significant point, clearly established by our work, was at first missed, in fact denied.[6] I have reference to the capital fact that vitamin K (all forms—some better than others) can counteract the action of Dicumarol.* I emphasized this in letters, personal conversations, and in my first lecture on Dicumarol at the Mayo Clinic and at Wisconsin General Hospital. In spite of these efforts the first clinical reports carried the statement that "vitamin K has no effect as an antidote to the administration of Dicumarol." The editorial and annotation writers for the medical journals, those who only "think" but "don't try," innocently reiterated this statement.[1, 2] While in error, the clinicians were in good company, for an authority on blood coagulation[16] had written in 1937, and again in his book published in 1942, that "vitamin K will not restore the prothrombin concentration" depleted by Dicumarol.[17]

Originally these denials made me very unhappy. The misfortune of being accused of error was not the primary basis for the unhappiness, for we were certain that the antidotal capacity of vitamin K would in time be sustained in the clinic. What did disturb me was the needless induction of the hemorrhagic "sweet clover disease" in man and the stigma temporarily attached to Dicumarol, that it was a dangerous drug.[18] *And this did happen.*

A feature of science that has always appealed to me is that sooner or later, and usually sooner, "the truth will conquer."

Dr. Shepard Shapiro in New York City was the first clinician (February 1942) to sustain our claims that vitamin K can counteract the anticoagulant action of Dicumarol in man when liver function is adequate.[5, 20] Subsequently he was independently supported by Townsend and Mills in Canada,[21] Lehman in Sweden,[22] and finally by Cromer and Barker[23] at the Mayo Clinic, as well as others. Today it is accepted that the water-soluble forms of vitamin K or vitamin K_1 given orally can successfully antidote overdosing with Dicumarol, provided they be employed when reversal is still possible.

Let us briefly examine why the error arose. The clinicians did not use a 1-stage prothrombin assay as sensitive as the one Campbell developed for our experimental animals. They were originally conditioned to the low levels of vitamin K effective in obstructive jaundice, biliary fistula, cholemic bleeding, etc. It was also thought that the menadione form of vitamin K might be toxic. Over 10 years were required to wipe out this error from clinical practice.

To summarize, surmise, faulty thinking, and not enough trying kept vitamin K from being the corner building stone in Dicumarol therapy that it deserved to be from the outset.

In 1950 Marple and Wright (pages 149 and 181)[6] wrote, "When bleeding occurred from the clinical use of Dicumarol the fault rested with the physician who administered the drug."

Enthusiasm—Muddle—Consolidation

Within 2 years after Dicumarol was synthesized, over 100 related 3-substituted 4-hydroxycoumarins were prepared in my lab-

*For an account of how, in January 1939, a bull desperately sick from eating spoiled sweet clover hay (he was "down," blood was oozing from the nose, and a massive hematoma adorned the right thigh) was rescued from the clutches of death via a vitamin K_1 concentrate prepared from alfalfa hay, see reference 2. Originally not even this "bull story" could break the bonds of the usual pattern of thought. The equation is

$$\text{Normal bull} \underset{\text{Vitamin } K_1 \text{ concentrate}}{\overset{\text{Spoiled sweet clover hay}}{\rightleftharpoons}} \text{Bleeding bull}$$

a completely reversible reaction.

oratory. Synthesis ran substantially ahead of biochemical appraisal. Accordingly, when I gave the Harvey Society lecture on "The Anticoagulant from Spoiled Sweet Clover Hay" in January 1944[1] it was indicated that "it would not be valid to conclude from the relative appraisals on activity made with the rabbit—that Dicumarol is the most desirable compound for clinical use." It was indicated that "In the course of the routine appraisal of the many compounds tested it was learned that some of them exhibited a slower but more sustained hypoprothrombinemic action, while the action of others is of shorter duration. It will take some time before final judgment can be passed on this subject. From the experience gained with other pharmacological agents it is abundantly clear that the final test is the action in man under a variety of conditions. The unpredictable can be surprising, so, as we see it, we might now be at the beginning of things and not at the end in this field of study."

Being an agriculturist I have little confidence in predictions, including my own. The situation can now be appraised in the light of wisdom after the event. Bear in mind that the statement quoted was made less than 4 years after Dicumarol became known to us and before extensive clinical information on the response in man was available. About 50 reports on the clinical use of Dicumarol had appeared between 1941 to 1944.[5, 6*]

The appearance of any new drug creates an interesting cycle of events, and Dicumarol went through that cycle quite rapidly. The first preliminary reports indicated that an atmosphere of optimism prevailed. They evoked prompt favorable editorial comment in the Lancet (September 13, 1941) under the title, *"Heparin and a Rival."* Then came the second period—a period of muddle. Enthusiasts and skeptics for anticoagulant therapy with Dicumarol were created, and it can be stated that some of the skeptics condemned the drug in no uncertain terms, though they were largely armed with surmise, faulty, or no prothrombin clotting time determinations and they used the antidote vitamin K inadequately. Then came the third period of consolidation, from which it can now be concluded that a better anticoagulant of the Dicumarol type was desired.

Since Dr. Wright asked for aspects of human interest, let me add another slice from the Dicumarol story. Early in September 1945 I was fed up with laboratory work, etc., and I went off on a canoe trip with my family. On this trip we were caught in a cold rain storm. I got soaked and overexhausted. Two weeks later I came down with what I had had once before—after a similar heavy physical bout, as a student in Switzerland—wet pleurisy. At first my doctor thought I had pneumonia; then I told him about my previous bouts of tuberculosis; so the diagnosis was changed to reactivated pulmonary tuberculosis. I spent 2 months at Wisconsin General Hospital and then was transferred to Lakeview Sanatorium headed by the double cross of Lorraine. Here I was supposed to vegetate like a topped carrot. I did rest there, physically for 6 months, took nothing stronger than cod liver oil and 3 bottles of beer a day, but kept the aged tuberculosis out of my mind by studying laboratory records and reading the history of rodent control from ancient to modern times.[24, 25]

A "Janus" in the Coumarin Family

Now brace yourselves, for I propose to shift from a "cow poison" that had become a drug of substantial clinical usefulness, to a "rat poison" converted to a drug, which has I believe most of the desirable features that can be expected from an anticoagulant to be given primarily via the oral route.

*The first clinical report to appear was by Butt, H. R., Allen, E. V., and Bollman, J. L.: *Preparation from spoiled sweet clover (3,3'-methylene-bis-4-hydroxycoumarin) which prolongs the coagulation and prothrombin time of blood: Preliminary report of experimental and clinical studies,* Proc. Staff Meet. Mayo Clinic **16:** 388-395 (June 18), 1941. See also Allen, E. V., Barker, N. W., and Waugh, J. M., J.A.M.A. **120:** 1009, 1942; Wright, I. S., and Prandoni, A., J.A.M.A. **120:** 1015, 1942; Bingham, J. B., Meyer, O. O., and Pohle, F. J., Am. J. M. Sc. **202:** 563, 1941.

The many coumarins synthesized between 1940 and 1944 were listed by numbers in logical groups based on their chemical structure.[1] While I was in the sanatorium in 1945-1946 the laboratory work was practically at a standstill. There were few students available, since most of them were still in the armed forces. So I had ample time to reexamine all the chemical and bioassay data available. Upon the return of L. D. Scheel from service in the spring of 1946, he was assigned to the task of reappraising the anticoagulant activity of the compounds numbered from 40 to 65. They were made by Ikawa in 1942-43. Instead of using only rabbits for the bioassays Scheel also used rats, mice, and dogs. In 1946-1948 he defined coumarin numbers 42 and 63 as being much more potent than Dicumarol in the rat and dog, as capable of producing a more uniform anticoagulant response, and as having the quality of maintaining a more severe state of hypothrombinemia without inducing visible bleeding. Certain chemical properties were also considered: the degree of purity readily attainable (absence of taste and odor), the cost of making them, and the property of being convertible to stable water-soluble salts.

Back in 1940 to 1942, Overman, Field, and my colleague, C. A. Bauman, had studied extensively the action of Dicumarol in the laboratory rat, and the effect of diet on the response, specifically the influence of vitamin K and foods rich in it. Later in 1942 I personally, with the help of good old Schoeffel, set up field trials to ascertain the suitability of Dicumarol for rodenticidal purpose. It was concluded that the activity of Dicumarol in the rat was not high enough to make it practical for rodent control. This was found to be largely due to the vitamin K content of mature grains and the availability of green foods with a high vitamin K content. It was shown that rats could tolerate a daily intake of 2.0 mg. of Dicumarol for 60 or more days due to the vitamin K content of the natural foods available. On a semisynthetic diet essentially free from vitamin K the survival time was about 15 to 23 days. When 5 mg. of vitamin K per day were added to the artificial diet, the rats also tolerated 2.0 mg. of Dicumarol daily for over 60 days.

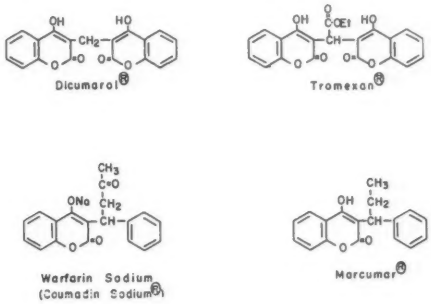
Early in 1948 I told Scheel and Dorothy Wu that I wanted to propose no. 42 for rodenticidal use.[24, 25] This proposal shook the laboratory. I can sum up by stating the consensus of opinion "the boss has really gone off the deep end this time." Scheel favored no. 63 for clinical purposes. They are chemically closely related, no. 63 being a direct derivative of no. 42. To make a long story very short, early in 1948 no. 42 was promoted for rodent control under the auspices of the Wisconsin Alumni Research Foundation through the able, enthusiastic, and public-spirited Ward Ross, General Manager of this organization. Within a short time this effort revolutionized the art of rodent control (multiple doses as opposed to the single dose of the highly toxic poisons), and warfarin rapidly became and still is the leader in the rodenticide field.* The name Warfarin was coined by me by combining the first letters of the Wisconsin Alumni Research Foundation with the "arin" from coumarin—and it is now a household word throughout the world.**

Between 1948 and 1952 Dicumarol was, so to speak, being squeezed by chemical kin stemming primarily from European studies.[26] "Imitation is the sincerest form of flattery." Curiously, one of them, a derivative of Dicumarol, trade-named Tromexan, was not seriously considered by us as early as 1940. Though it acted somewhat faster than Dicumarol, it required substantially larger doses

*Just as cattle eat hemorrhagic sweet clover hay until they die without visible sensory responses, the rat eats warfarinized cereal grain bait until fatal hemorrhage sets in. Neither bait refusal nor bait shyness develops. Indeed, the rodent's departure is biblical "death without sting." In Maxwell Anderson's drama, Elizabeth the Queen says, "To the end of time it will be so . . . the rats inherit the earth." Since warfarin has become available, this need not be so. Furthermore, via the water-soluble warfarin sodium the rat can drink unto death.

**Warfarin is the safest rodenticide known. Up to now, in the United States there is no recorded case of a warfarin-induced fatality in man, although over 140,000,000 pounds of warfarin containing bait (0.025 per cent) have been distributed since 1950.

o get the equivalent anticoagulant action.* The second, Marcumar, a close kin to warfarin, vas also passed by us, since its water-soluble odium salt is less stable than warfarin so- lium. Milligram for milligram, Marcumar is nore active than warfarin and its action is lso more prolonged. But as a result of the laims made about Tromexan and Marcumar I took another good look at the mass data in the light of what clinicians were seeking, namely an anticoagulant that could be used via any route with the retention of the virtues of Dicumarol but without its limitations.



Based in part on the supposition that the response of the rat to warfarin (no. 42) was a very reliable index of how man would respond, late in 1950 I told Dr. S. Shapiro and Dr. O. O. Meyer that the water-soluble sodium salt of warfarin should be tried on man. In 1941 the clinicians had literally snatched the "cow poison" from us, but the transition to a substance originally promoted to exterminate rats and mice was a bit more than they could accept with real enthusiasm. Then, on April 5, 1951, we were informed by Captain J. Love (MC) in the U.S.N. at Philadelphia that an army inductee was admitted to the Naval Hospital who had taken over a period of 5 days a concentrate of warfarin designed for rodent control.[27] The package contained 567 mg. of warfarin in corn starch. The inductee had followed the multiple dose directions on the package. It became clear to him that warfarin was not an efficient agent "to shuffle off" this "mortal coil." It allowed too much time for thinking—so he went to the hospital with a fully developed case of hemorrhagic "sweet clover disease." He was treated per the directions—blood transfusion and large doses of Vitamin K—and made an uneventful recovery.[28]

This incident acted as a catalyst. Shapiro[29] and Meyer[31] both concluded from their carefully done work with warfarin sodium that it did possess certain properties not inherent in Dicumarol or the other anticoagulants they

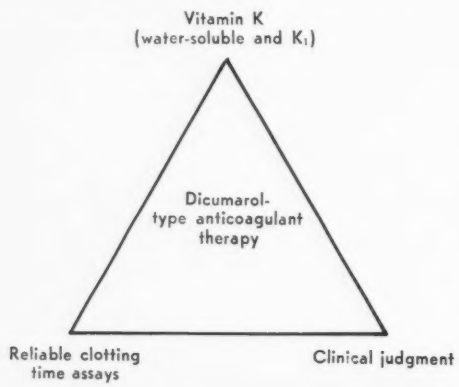
*The clinical promotion of Tromexan (bis-3,3'-4-xycoumarinyl) ethyl acetate, referred to as B.O.E.A. n the article by Burt, C. C., Wright, H. P., and Kubik, M., Brit. M. J. 2: 1250, 1949, precipitated nteresting editorial comment under the heading, *Dangers of Dicumarol* (pp. 1279-1280). In this edi- orial it was suggested that since Tromexan seemed o be superior to Dicumarol "owing to its shorter- ived action . . ." and in view of recent reports of he drug's (Dicumarol's) efficiency as a rat poison, t may be that Dicumarol will ultimately be more seful for that purpose."

Unfortunately the significance of our paper on the ction of Dicumarol in the rat dealing specifically with the effect of diet and vitamin K on the anti- coagulant action (J. Nutrition 23: 589-602, 1942) was not appreciated by O'Conner, J. A., Research 1: 334, 1948, who suggested the use of Dicumarol for rodent control. Had O'Conner read our paper carefully, he would not have made this suggestion. The critical issue is that Dicumarol's anticoagulant action in the rat subsisting on natural grain foods is too slow to be practical. The level of Dicumarol in the bait has to be set so high that other animals (cat, dog) and children (accidental ingestion) would be vulnerable.

It was the inefficiency and slowness of Dicumarol to kill rats under practical field conditions that caused me not to suggest its use as a rodenticide in 1941-1943 (letter, Link, K. P., to the National Defense Research Council, Washington, D.C., dated March 19, 1943, and confidential disclosures, 1942-1943, to the late Professor Homer Adkins and Professor H. Gilman, official investigators and project leaders of N.D.R.C. and O.S.R.D. (confirmatory letter of Gilman to Link, June 11, 1952). Instead of Dicu- marol the much more potent and efficient (no. 42) warfarin was recommended. Nevertheless, O'Conner's paper served a useful purpose in rodenticide control circles, and he must be accredited with being the first one to stimulate, via the printed page, the backward pest control workers by pointing out the potentials of anticoagulants (Link, K. P., letter December 6, 1948, to U.S.D.I. Fish and Wildlife Service, Denver, Colo.). I had attempted to create an interest in warfarin via letters and memoranda, which at first failed to reach the objective (see reference 24 and particularly reference 25). A complete history of the warfarin development based on 10 years of practical field experience is in the process of being prepared.

had tried. After Collin Schroeder perfected the process of making warfarin sodium, I induced my long-standing friend, Dr. S. M. Gordon, of the Endo Laboratories, Richmond Hill, N.Y., to make it available for clinical use. This he did, under the trade name Coumadin Sodium. Today it would appear, from the 15 to 20 clinical papers on warfarin sodium that have been published (see reference 32), that most of the drawbacks of Dicumarol have been overcome. Warfarin sodium is at least 5 and possibly 10 times more potent than Dicumarol. It is the only synthetic anticoagulant available today for therapeutic anticoagulation that can be given orally, intravenously, intramuscularly, or rectally.[32] The rate of absorption is almost the same, irrespective of how it is administered. No other anticoagulant of the Dicumarol type has all these virtues. Of course, an overdosage can be readily corrected via vitamin K. It acts faster than Dicumarol, and fewer prothrombin times are required in its routine use. To use the words of both Shapiro and Meyer, "It is easier to handle clinically." It is my firm belief that in time it will replace Dicumarol on the basis of its performance over a wide variety of conditions and that other anticoagulants of the Dicumarol type will not be superior.

It always seems appropriate to me to visualize successful anticoagulant therapy with the Dicumarol-type drugs as being shaped like a triangle with accurate "prothrombin assays" at one corner, vitamin K at another, and sound clinical judgment at the third.



Each corner is linked to the other by way of the connecting sides. There should be no separation, each is vitally dependent on the other two. Though the clinical judgment be good and the "prothrombin time" accurate, the vitamin K corner might still have to be evoked, since each individual patient is essentially "an unstandardized biologic entity," errors in dosage can be made by the hospital service, the patient might have a silent ulcer, or the functioning of the *liver* or *kidney* might unknowingly be penumbral.

On September 29, 1955, I got a card from a former Wisconsinite working in Fitzsimons Army Hospital in Denver, Colorado which read, "The President is getting one of your drugs and it's not Dicumarol." A day later press secretary J. C. Hagerty announced,[33] "The heparin which was used initially as the anticoagulant has been replaced by a drug of the Dicumarol type. The present prothrombin level has been well maintained." I knew of Colonel Pollock's paper, "Clinical experience with warfarin (coumadin sodium a new anticoagulant)," read before the first annual meeting of the American College of Angiology Atlantic City, N.J., on June 4, 1955, and I surmised that the most important man in the world today was being anticoagulated via warfarin sodium.[34] This surmise proved to be correct and since then it is an open secret that warfarin sodium was being used. *"The unpredictable can be surprising."*

In closing I wish to indicate that what my laboratory has achieved in the past 2½ decades represents the combined effort of many students. It is fun to be the reporter or narrator of this highly successful adventure. To use the words of the late Allan Gregg,[35] my students represented much "emergent ability." I think the secret of their success is 3-pronged: they never ceased to wonder, they kept on trying, and they were on a project directed toward doing mankind *some good* instead of trying to *destroy it*.

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The Introduction of Heparin Therapy in Cases of Early Thrombosis

By GUNNAR BAUER, M.D.

THE CURRENT METHOD of combatting acute deep venous thrombosis of the leg by means of very early diagnosis, intermittent intravenous injections of heparin, free movements of the affected limb, and early ambulation was, I believe, first used at the Mariestad Hospital, Sweden, where it was introduced on October 1, 1940. I shall give a brief account of the events that led up to this scheme of treatment.

Being originally interested in the clinical and roentgenologic study of blood vessels, I was impressed by an article published in 1938 by Cid dos Santos,[1] describing a technic for introducing x-ray contrast medium into the deep veins of the leg. After having made some modifications to adapt it for clinical purposes, I found that it provided a reliable method for studying roentgenologically the deep veins of the lower leg in particular. When the normal anatomy had been established, the pathologic changes brought about by thrombosis were studied. It soon became evident that the whole of the thrombotic process, from the first beginning to the final stage, could be followed in a way that had not earlier been possible.[2, 3]

The matter of principal interest in the present connection is the fact that it could be shown that the thrombotic process almost invariably (in 96 to 98 per cent of the cases) originates as a small adherent thrombus in one of the deep venous trunks of the lower leg. At that time, it was generally believed that the process first appeared in the pelvic or femoral veins. That it actually started in the calf was suspected by a few, but no evidence could be produced. With the aid of phlebography, the question was now settled beyond doubt.

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Comparing the x-ray findings with clinical data, I was able after some time to single out the faint clinical symptoms associated with the early stages of intravenous thrombosis, and presently I found that it was possible to diagnose leg thrombosis at a much earlier stage than had hitherto been possible. There was no need to wait for pain and milk leg to appear. The process could be detected when it was still localized to the lower leg, i.e., in its statu nascendi.

This was a point won, but it did not bring us one step nearer to helping the afflicted patients. In fact, we found ourselves, in 1939 and the beginning of 1940, in a somewhat anomalous position. Although we knew how to diagnose thrombosis in its initial stage, we were unable to prevent the process from following the path we knew only too well it would take. During this period we were faced on 29 occasions with cases in which phlebography disclosed the presence of incipient thrombosis of the lower leg. Since no effective therapy was available, we had the painful experience of remaining inactive and seeing how, in 24 cases, the process spread after 1 or 2 days to the femoral vein, and brought about a phlegmasia alba dolens. In 5 cases there was propagation to the large pelvic veins, and in 10 cases the other leg as well was attacked by thrombosis. Pulmonary embolism developed in 11 cases, 2 of which were fatal. The result would probably have been the same in another 2 cases with repeated pulmonary infarcts if recourse had not been made to ligation of the femoral vein.

These incidents, although not more remarkable than in any other thrombosis material at that time, seemed to us to be particularly deplorable, because we were able to observe and record every step in the deterioration of the cases.

It was in this position that we decided to make a trial with heparin.

Concerning this drug, a fair number of facts, exhaustively reported by Jorpes,[4] and Crafoord and Jorpes,[5] had accumulated at that time. Reviewing them, we concluded that prophylactic therapy could be ruled out as a routine method, and also that treatment of fully developed thrombosis had not yielded fully satisfactory results, even if Murray[6] had been fairly successful in a series of cases of embolism or thrombophlebitis. However, being in possession of a method for diagnosing thrombosis at an earlier stage than had formerly been possible, it occurred to us that if heparin were to be introduced at such a stage, better results might be expected. Accordingly, after cooperation with Jorpes and Crafoord as to the size of the heparin doses, we started treatment along these lines on October 1, 1940. Heparin was given intravenously 3 or 4 times a day, the doses varying between 100 and 150 mg. in each injection. Free movements of the leg were encouraged, and the patients were allowed out of bed as soon as the acute symptoms had subsided.

The results were favorable from the outset, and the entire course of the disease was found to be completely changed. No spreading of the thrombotic process occurred, and fever, swelling, and pain disappeared in a surprisingly short time. The patients were, as a rule, able to leave their beds in less than a week, completely healed. The mortality at once fell to less than one tenth of the earlier figure.

As the aforementioned mode of action was also found to involve little or no risk to the patient in the form of hemorrhagic or other complications, and because it became evident that the necessary heparin doses could easily be fixed without any determinations of the coagulation time, it was decided to continue along the same lines. Thus, the method has been used for more than 17 years, without any modifications.

During this period, the results have been reported at various intervals.[7–13] At the time of the most recent publication,[13] they were as follows. Heparin therapy was given in altogether 627 cases of thromboembolism. Five deaths occurred; the mortality was thus 0.8 per cent. In 622 cases, the course during treatment was mainly uneventful. The mean duration of recumbency was 4.4 days. Complications were infrequent. A recurrence took place in 17 cases (2.7 per cent) and a slight hemorrhagic tendency was noted in 13 (2 per cent). Pulmonary embolism was present in 45 patients before the institution of treatment; all except 2 recovered.

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Experience with Anticoagulants

By Irving S. Wright, M.D.

THE GREAT STUDIES of Schmidt, Morawitz, Virchow, Rokitansky and others on the pathogenesis of thrombosis and embolism produced no specific clues leading to a sound method of treatment for these deadly and disabling complications of disease.[1] Just 24 years ago Morawitz made the following statement. "Even today it is still a thankless task to discuss the problem of thrombosis on the sickbed; thrombosis has lost none of its danger; it is still a fearsome disease, a frightening spectre to the surgeon and the physician. We still seek vaguely hither and thither for prophylactic and therapeutic measures." To one working in the field of cardiovascular diseases, the lack of agents with which to combat the thrombosing process was a constant source of frustration. Heparin was theoretically available after McLean's[2] discovery and Howell's early work[3] but actually this was not true because of the difficulty of preparation, the impurity of the product, the severe reactions which forbade its use in man, and the great expense involved in producing small amounts. It was therefore an interesting tool for the laboratory but not safe for man. Best, Scott, and Charles had taken the first major step toward producing a heparin suitable for use in man in 1934, but it was not available for general use for another 5 years. When, therefore, in 1938 I lay in bed for 4 months harassed by a severe thrombophlebitis which occurred after an appendectomy, and which finally burned itself out after producing almost daily fevers of 102 to 103 F. and a total loss of 60 pounds in weight, I had both time and special cause for contemplation on this subject. The same year we learned that Best and his co-workers[4, 5] had succeeded in producing satisfactory heparin in sufficient quantities so that it could be used in the treatment of thrombosis in man without the risk of severe reaction, provided careful control of the clotting time was observed.

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In the fall of 1938 a young man (A. S.), aged 31, was seen in consultation with Drs. Leo Mayer and Jerome Marks. He had been suffering from an intractable and migrating thrombophlebitis which had involved the veins of the legs and the superficial veins of the trunk. In addition, there was clinical evidence of involvement of the mesenteric, splenic, renal, and probably pulmonary venous systems. Available treatment had failed to change the progressive course of this disease. Drs. Best and Murray generously agreed to come to New York, sharing some of their limited supply of heparin, and to help us set up the continuous intravenous infusion with suitable controls of the clotting time. For 16 days and nights during which all concerned were constantly apprehensive, the infusion continued with clotting times being taken at 2 to 4 hour intervals. There were no untoward incidents. The temperature, which had been elevated daily for months, remained normal throughout and the existing lesions subsided. No new lesions developed. This was most encouraging. At the end of that period our supply of heparin ran out and Dr. Best had no more to give us. Unfortunately, shortly thereafter the patient's fever returned and the course of the disease continued uninterrupted until some months later, when he contracted mumps from one of his children, became very ill, and developed a fever that reached 106 F. This fell to normal by crisis, after which the phlebitis disappeared and did not recur for several years. This was never explained, but the experience with heparin was sufficiently interesting for us to use it in additional patients. This was believed to be the first patient treated with the improved heparin in the United States although a few had received it in Canada.

As we were able to obtain additional supplies of heparin, we tried it on other patients, but the cost and difficulty of maintaining continuous intravenous infusions, the only method recommended at that time, was such that it

was not very practical for general use. The need for an anticoagulant that could be administered orally and that was not too costly became increasingly apparent.

Meanwhile, Karl Paul Link and his coworkers had been working for some years in an attempt to isolate the compound that was present in spoiled sweet clover. This factor had been recognized by the 2 veterinarians, Schofield and Roderick separately, as the cause of a hemorrhagic disease in cattle. The substance responsible for this phenomenon had never been isolated. Link's experiences will be found in his paper in this symposium.

Beginning in 1940, Karl Paul Link and his co-workers began to publish a classical series of papers on this subject and this was capped in April 1941 by the report of the identification and synthesis of the hemorrhagic agent.[6] This was truly exciting and we immediately wrote asking Dr. Link for supplies of this new synthetic agent as soon as he could spare some. His response was prompt and generous and shortly thereafter we began to receive supplies of the first oral anticoagulant, which was suitable for use in man, Dicumarol. Link had, previous to his publication, supplied some Dicumarol to O. O. Meyer, J. B. Bingham, and F. J. Pohle at the University of Wisconsin where he worked, and to H. R. Butt, E. V. Allen and J. L. Bollman at the Mayo Clinic. On February 27, 1941, Meyer presented the first report on its use in man at the University of Wisconsin.[7] In June 1941, Butt, Allen, and Bollman[8] published a preliminary study of its use in dogs and in a series of 6 human beings. In October 1941, we presented our preliminary experiences with its use in 20 human beings.

Immediately upon receiving the first shipment of material from Dr. Link, Dr. Andrew Prandoni, who was working with me as a research fellow, and I set up a program to test it in man at the Goldwater Memorial Hospital.[9] While recognizing the potential risk as seen in animals, neither of the previous groups had reported any hemorrhagic complications in man. We soon encountered some of considerable severity. For example, one patient who leaned out of bed developed a subcutaneous hemorrhage on 1 flank about 8 inches in diameter. Others developed hematuria. This was naturally alarming and both Dr. Prandoni and I lost much sleep over this, but resolved to continue the studies. As it turned out, this was a significant observation, since several pharmaceutical houses were then ready to release large amounts of this substance on the market without adequate understanding or warning regarding the risk and with no detailed knowledge of how to handle such complications if they occurred in man. This would have made it available to physicians without proper training for this form of therapy who would in turn have been dependent on laboratories where the tests for prothrombin time were totally inadequate for measurement of the activity of this potent but potentially dangerous new drug. With the cooperation of the Council of Pharmacy of the American Medical Association and the pharmaceutical houses, the release was delayed until further studies could be carried out. This was actually a matter of more than a year. It is probable that many tragedies were averted by this cautious step . Why did our patients develop hemorrhages whereas the others had not thus far encountered this complication? We finally concluded that this was because we used the Russell Viper Venom technic for our prothrombin tests. This was an accepted method at that time but was not sensitive enough to measure early changes in factor VII and prothrombin activity and since the dosage of Dicumarol in man was uncertain, this presented real danger. Another disturbing factor was finding that the dosage of Dicumarol could not be determined on the basis of the weight of the patient. Lastly, we found that the poorly nourished, often cachectic, patients we worked with did not react to Dicumarol in the same way as the well nourished patients of the Wisconsin and Minnesota groups.

Communication with Drs. Meyer and Allen made it possible for us to cross check our results. On May 4, 1942, Drs. Meyer and Allen and I, each representing our respective teams, presented data before the American Society for Clinical Investigation and this

was repeated in greater detail before the Section on Experimental Medicine and Therapeutics of the American Medical Association in June 1942.[10-12] The experiences were so similar and encouraging that coming from 3 separate institutions the impact was such as to stimulate others to initiate broader studies. We had an effective anticlotting agent which could be administered by mouth, but now the challenge was to determine the indications and contraindications for its use in the care of patients. The experience in numerous hospitals with its use for the prevention and treatment of thrombophlebitis and pulmonary embolism was rapidly and favorably developed. In May 1942 we started to use it cautiously in patients with heart disease, first for myocardial infarction with embolization, then with rheumatic heart disease with embolization. The patients tolerated the drug well and the clinical impression was encouraging but the material was limited because of the lack of confidence in this form of therapy by others as well as ourselves.

World War II then entered into the picture and undoubtedly delayed the development and acceptance of anticoagulant therapy, since many who were active in this field entered the armed forces. Although we could not obtain official approval from the Surgeon General's Office to stock Dicumarol in Army pharmacies until later, we did succeed in getting tacit permission to continue our studies first at the Army and Navy General Hospital in Hot Springs, Arkansas, and later in numerous army hospitals in the Midwest and and Far West where I served as consultant. Dr. Prandoni also continued to increase his experience with anticoagulants on the Medical Service at the Walter Reed Hospital.

By 1945 we had accumulated data based on the treatment of 76 patients suffering from acute or recurrent myocardial infarction, and this was reported before the California Heart Association on October 18, 1945.[13, 14]

Meanwhile, E. S. Nichol and S. W. Page of Miami, and H. R. Peters, J. R. Guyther, and C. E. Brambel of Baltimore had been accumulating series of patients suffering from myocardial infarction treated with Dicumarol. Their experiences were published early in 1946 and were in agreement with ours.[15, 16] This was encouraging but the data were not conclusive and we therefore proposed the cooperative study which was carried out by the Committee on Anticoagulants of the American Heart Association. The report of this committee includes the details of its work. This large project enlisted the resources of 16 leading medical institutions with teams of workers each headed by an outstanding cardiologist. A central laboratory and statistical center at the New York Hospital acted as the coordinating agency. Cases admitted on alternate days were admitted to treated and controlled series. Master forms were compiled in detail and analyzed by Dr. Dorothy Beck, Chief Statistician, and her staff. In 2 years the case records of 1,031 patients were secured. Preliminary reports were issued, but the final report took more than 6 years to complete.[17, 18] Following the publication of this report the use of anticoagulants for the treatment of myocardial infarction was adopted widely in many countries as well as in the United States. Although there still exist some differences of opinion regarding the selection of suitable cases, there have been more than 60 confirmatory reports published from medical centers in this country and abroad and the wide use of this form of therapy seems to be accepted for the foreseeable future.

There are now many anticoagulants of the coumarin and phenylindandione groups available. We have evaluated a number of them. They vary somewhat in onset and duration of action but present few advantages over Dicumarol and phenylindandione as they were first made available for general use.

As indicated above, in 1942 we began the treatment of patients with multiple embolization from old rheumatic heart disease and myocardial infarction. Thus evolved the conception of long-term anticoagulant therapy. Some of these patients had developed cerebral emboli and it seemed logical to attempt to interrupt a tragic series of events leading to death or perhaps even worse, complete invalidism. From these experiences we were encouraged to treat patients with cerebral

thrombosis including carotid artery and basilar artery thrombosis. This was seriously embarked upon in December 1946 and the results have been reported at intervals since that time.[19] This work has expanded and is now being submitted to analysis in several cooperative long-term studies in which our group is actively participating. Great credit is due to Dr. William T. Foley and Dr. Ellen McDevitt for their consistent work in this field during the past decade.[20-23] The final evaluation of the indications and contraindications for the use of anticoagulants in the treatment of cerebral thrombosis remains to be concluded during the coming years.

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Historical Data Regarding the Experiences with Coumarin Anticoagulants at the University of Wisconsin Medical School

By Ovid O. Meyer, M.D.

IT WAS 1938, 20 years ago, when, in conversation with Professor R. A. Brink of the Department of Genetics at the University of Wisconsin, that I first heard of the work being done in the Department of Agriculture to identify the substance in spoiled sweet clover accountable for hemorrhagic disease in cattle. This had been initially undertaken in 1934 at the Wisconsin Agricultural Experiment Station by Professor Karl Paul Link and his associates. This group of workers, including Campbell,[1] Stahmann and Huebner,[2] finally isolated the anticoagulant, a coumarin derivative, and established its chemical characteristics. The yield was about 1 Gm. per ton of clover, an amount which was not practical for clinical usage. However, by April 1940, these investigators had synthesized a 3-substituted-4-hydroxycoumarin which was chemically, physically, and biologically identical to the naturally occurring substance. This could be prepared cheaply and in abundant quantities. The potential significance in the treatment of thromboembolic disease was then obvious, and hence we were happy when a supply was made available to us for basic studies in September 1940. The anticoagulant for clinical purposes was given the name Dicumarol.

My early associates in the field included James B. Bingham, now in Seattle, Dr. Frederick J. Pohle, deceased, Dr. John McCarter, now of Boise, Idaho, Dr. Charles T. Thill of Chicago, and Dr. Maryloo Spooner Schallek of Nutley, N. J. It was promptly established that this anticoagulant was a potent hypoprothrombinemic agent in vivo in dogs and without effect in vitro. Our original experiments were set up to elucidate the morphologic changes that might occur in dogs when so-called therapeutic and toxic doses were given, to establish the range between the effective therapeutic dose and the minimal lethal dose, to determine whether or not this anticoagulant reduced the prothrombin in human beings as it had been shown to do in cattle, rabbits, rats, mice, guinea pigs, and dogs, and to demonstrate whether administration of this dicoumarin in safe dosage would actually prevent or prolong the time of intravascular clotting. The final and most important objective, of course, was to establish whether or not the anticoagulant would prevent the development of thromboses in human beings. investigation of the above effects was mainly directed toward this major aim, which obviously could be settled "only by extensive investigations of the future."[3]

Our first published report[3] established that the administration of oral (the powdered substance given in a gelatin capsule)* or intravenous administration of Dicumarol produced, after a usual latent period of 24 hours, prolongation of the prothrombin time (and coagulation time if measured at room temperature but not if properly measured in a water bath at 37-38 C.). It was further demonstrated that therapeutic and even fatal doses did not produce significant pathologic changes in the liver or other parenchymal organs. It was shown[3, 4] in dogs, however, that excessive or fatal, but not therapeutic, doses produced

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*3,3'-methylenebis (4-hydroxycoumarin) is highly insoluble in water. At a pH of 10 or more the sodium salts are soluble but the solutions are unstable and must be used promptly after being prepared.

hemorrhages, gross or microscopic, toxic lesions, and marked dilatation of small arteries, arterioles, capillaries, venules, and small veins, acute renal glomerular swelling, and toxic lymphoid degeneration. These effects are emphasized, since several authors, at least by implications, have indicated that Dicumarol is a vasodilator, which it is not unless toxic doses are administered. We have never observed vasodilatation when proper doses are employed.

After gathering, with a less than ideal method, some suggestive experimental evidence that Dicumarol did prevent some intravascular (jugular) clotting in dogs[3] and after establishing the safety of the drug in animals and an approximately proper dosage, we cautiously administered it to human beings to achieve the data needed for clinical use. The first 12 patients who received the drug were, with 1 exception, patients with advanced malignancy. The patients, save 1, demonstrated no definite clinical evidence of involvement of the liver. The very first patient received a total dose of 10 mg. and the other 11 patients received doses of 50 to 100 mg. (0.75 to 2.0 mg. per Kg.). In 5 of these 11 the prothrombin time was slightly prolonged. It was then promptly established in additional patients that a dose of 4 mg. per Kg. was safe and could produce significant hypoprothrombinemia. Still later[5] it was found that, in our hands, the most satisfactory therapy entailed the use of an initial oral dose of 5 mg. per Kg., followed by doses of 1.5 mg. per Kg., on those days when a dose could be given to maintain the prothrombin at 50 to 25 per cent. As is well known, subsequent studies by many others as well as ourselves have established that still lower levels of prothrombin are better.

The first public report of our experiences with this anticoagulant was made in the discussion of a paper presented by Professor Link before the University of Wisconsin Medical School Society, February 27, 1941.

By early winter, 1942, we had more clearly demonstrated, as had others,[6] the permissibility of giving the anticoagulant for as long as 6 weeks without toxic effect and the absolute need for daily or at least frequent prothrombin time determinations if the drug was to be safely administered. We found that blood transfusions appeared to be effective in controlling excessive hypoprothrombinemia and that vitamin K was ineffective, but we used doses no larger than 10 mg. given orally or intramuscularly. However, Shapiro et al.[7] demonstrated that vitamin K in relatively large amounts did counteract Dicumarol-induced hypoprothrombinemia and Cromer and Barker[8] found that large doses, 64 mg. of menadione bisulfite intravenously, usually were effective in correcting excessive hypoprothrombinemia due to administration of Dicumarol.

In 1943 we observed[9] that the rectal administration of Dicumarol in suppositories was not regularly effective. Miss Maryloo Spooner, while a graduate student at the University of Wisconsin, established, using the method of Helen Wright,[10] that Dicumarol decreased the adhesiveness of platelets without affecting the platelet count per se.

By 1943 there were several workers investigating coumarin anticoagulant therapy, and the practicality and usefulness of this drug became increasingly evident. It has been widely established that the only hazardous effect of this treatment was hemorrhage, and this was likely, of course, in patients who had ulcerative lesions, a hemorrhagic tendency, significant liver disease, or in the rare patient who was unusually sensitive to the drug in ordinary dosage. Some rare individuals were unusually resistant and required large doses. However, we sought a more ideal anticoagulant, a fixed dose of which would produce a fixed proportional hypoprothrombinemic effect, in order to avoid, insofar as possible, the need for frequent, troublesome, costly, and sometimes unavailable prothrombin time determinations.

Hence we were pleased to test another coumarin compound, 4-hydroxycoumarin no. 63, made available to us by Professor Link and Dr. Lester D. Scheel in May 1949. This synthetic chemical, 2-methyl-2-methoxy-4-phenyl-5-orodihydropyrano-(3-2c)(1) benzopyran,

was first tested in dogs, a dose was established, and it was later tested in human beings.[11] The results indicated that this anticoagulant was 2 to 3 times as potent as Dicumarol and that lethal doses in dogs did not produce the toxic lesions in the small blood vessels that occurred with excessive administration of Dicumarol. Although it appeared from these and later studies[12] that a greater stability of hypoprothrombinemic maintenance seemed possible with this drug (cyclocumarol) and that it had no apparent disadvantages, it never became popular, and in our own clinical work it was subsequently replaced when warfarin sodium was introduced. While testing this latter anticoagulant, we first observed that vitamin K_1 and vitamin K_1 oxide were very effective antidotes for excessive hypoprothrombinemia due to this and the other coumarin anticoagulants. James et al.[13] had previously reported this observation for vitamin K_1 oxide. Obviously this was an important addition to our armamentarium, since it appreciably lessened the hazard of coumarin anticoagulant treatment.

While testing this anticoagulant, we inadvertently learned of another hazard in this type of therapy.[14] In retrospect, it seems humorous, but it was not funny at the time and it might have been tragic. Two patients of the same name were on the same hospital ward. One was receiving the 4-hydroxycoumarin anticoagulant, and the prothrombin time determinations were carried out daily on the blood of the other. Since the former patient appeared to be resistant to this drug and the daily prothrombin of the latter was 100 per cent, the dosage was progressively increased, and only when subcutaneous bleeding developed at the site of hypodermoclysis needle punctures in the patient receiving the anticoagulant was the error realized and corrective measures taken. This was the fifth of 200 patients who demonstrated gross hemorrhagic side effects attributable to cyclocumarol.

The ideal anticoagulant had still not been discovered, nor has it yet. The toxicity of those available was low, and effectiveness was demonstrated. Nevertheless, it was still hoped that an anticoagulant with more regular response in prothrombin reduction to any given dose and with greater stability of levels of prothrombin might become available so that less frequent prothrombin determinations might be possible.

Synthesis of the 3-substituted-4-hydroxycoumarin anticoagulant no. 42, 3-(a phenyl-β-acetylethyl)-4-hydroxycoumarin, was first accomplished and its action studied in Professor Karl Paul Link's laboratory.[15, 16] This compound was named warfarin, and its readily water-soluble sodium salt was warfarin sodium. This anticoagulant was first kindly supplied by Professor Link and later by Dr. Samuel B. Gordon of Endo Products, Inc., Richmond Hill, N. Y. Initially in 1953 we used both warfarin and warfarin sodium, which are more potent than the other 2 anticoagulants. Later, since the former had no advantages, we continued our studies with only warfarin sodium, which we have found subsequently can be used intravenously and intramuscularly with safety, as well as orally.[17] To my knowledge, no other coumarin anticoagulant can be satisfactorily employed parenterally. In 1956[18] we found that, unlike Dicumarol, warfarin sodium was consistently effective when administered rectally. Our investigations demonstrated that this anticoagulant was superior, not only because it could be given parenterally if the need existed, but because the latent period, which was the same for oral and parenteral administration, was shorter than for either Dicumarol or cyclocumarol (Cumopyran). Even more important, with warfarin and warfarin sodium it has been easier to maintain the prothrombin level steadily within the therapeutic range. Hence, the staff throughout our hospital has found it generally easier to manage the patients requiring anticoagulant therapy. The hazards of anticoagulant therapy are the same for warfarin sodium as for other coumarin compounds, though perhaps somewhat lessened, and vitamin K_1 has been found to be a satisfactory antidote for the excessive hypoprothrombinemia which could result. In our

institution for the past 3 years Dicumarol and cyclocumarol have been almost entirely superseded by this newer coumarin compound.

This concludes my remarks, limited to the contribution of the investigators at the University of Wisconsin Medical School. These historical facts are related as accurately as possible in order to make our segment in the final historical profile complete and graphic. The total picture will point out the numerous contributions of many investigators in the elucidation of this very interesting subject. Once more there is emphasized the importance of fundamental progress from the laboratory of the scientist making the original discovery to the final successful clinical application. Obviously many unanswered problems remain in this field, and there is much opportunity for other workers to perfect the applications of the present information and to augment these facts with additional, much needed information.

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My Early Experience with Bishydroxycoumarin (Dicumarol)

By EDGAR V. ALLEN, M.D.

" . . . *leaven to quicken the blood that ran* . . . "
A. C. Swinburne, 1878

IN THE LAST of March 1941, my associate at the Mayo Clinic, Dr. H. R. Butt, gave a lecture at the weekly meeting of the staff of the Mayo Clinic on the use of vitamin K to correct deficiency of prothrombin associated with jaundice and disease of the liver. In the course of that lecture he mentioned a compound that had been prepared which was capable of producing a deficiency of prothrombin in animals. This state apparently could not be corrected by the administration of vitamin K. After the lecture I asked Dr. Butt about the new preparation, and found that he had read about it only a few days previously in the *Journal of Biological Chemistry*. The work had been done by Dr. Karl P. Link and his associates at the University of Wisconsin. Dr. Butt had been working with vitamin K and measurements of prothrombin for several years, and he was greatly interested in this new discovery.

A request was sent to Dr. Link for a supply of some material for clinical use. We discussed at some length the possible clinical uses of this material but, to the best of our knowledge, it never had been administered to a human being, so all we could do was to speculate. We did have high hopes. Dr. Link and his associates very promptly sent to us some bishydroxycoumarin (Dicumarol). A study of the effect of this compound on dogs was begun by Dr. J. L. Bollman about the middle of April 1941. The results of his studies confirmed the observations of Link and his associates.

My associates and I who were interested in intravascular coagulation had used heparin for a number of years. Heparin was known to be valuable in the treatment of vascular thrombosis and embolism, but it had disadvantages, specifically in its short action, its need for parenteral administration, and its considerable cost. I had believed for some time that another preparation could be used that would abolish these objections and that would be beneficial in the care of patients with vascular thrombosis and embolism.

On May 9, 1941, Dr. Butt and I administered Dicumarol to an organically sound young man who was 19 years old and who weighed 80 Kg. We had no alternative but to guess at the proper dose; we gave too much, that is, 1.8 Gm. in 5 days. On the sixth day after our patient first swallowed the Dicumarol, Miss Margaret M. Hurn, who was determining prothrombin activity in the blood, called me, with some concern, to say that our patient had almost no prothrombin in his blood (fig. 1). Moreover, the coagulation time of the blood was prolonged (fig. 2). Dr. Butt and I shared Miss Hurn's concern, for we were conscious of the possibility of severe hemorrhage.

Although at that time vitamin K was considered to lack the ability to increase prothrombin activity when deficiency of prothrombin was induced by Dicumarol, we gave the patient 20 mg. of synthetic vitamin K intravenously, at the suggestion of Dr. Butt. The prothrombin time decreased from 140 to 87 seconds within 24 hours, but at the end of another 24 hour period the prothrombin time was 161 seconds. It was only many months later, when reviewing the clinical record of the patient, that we recognized that there had been substantial increase in prothrombin activity attributable to the use of vitamin K. Until that time we had believed that the recorded change in prothrombin activity had been a "normal fluctuation." When we finally recognized, in retrospect, the specific effect of vitamin K on the blood of our patient, it had already been demonstrated that large doses of

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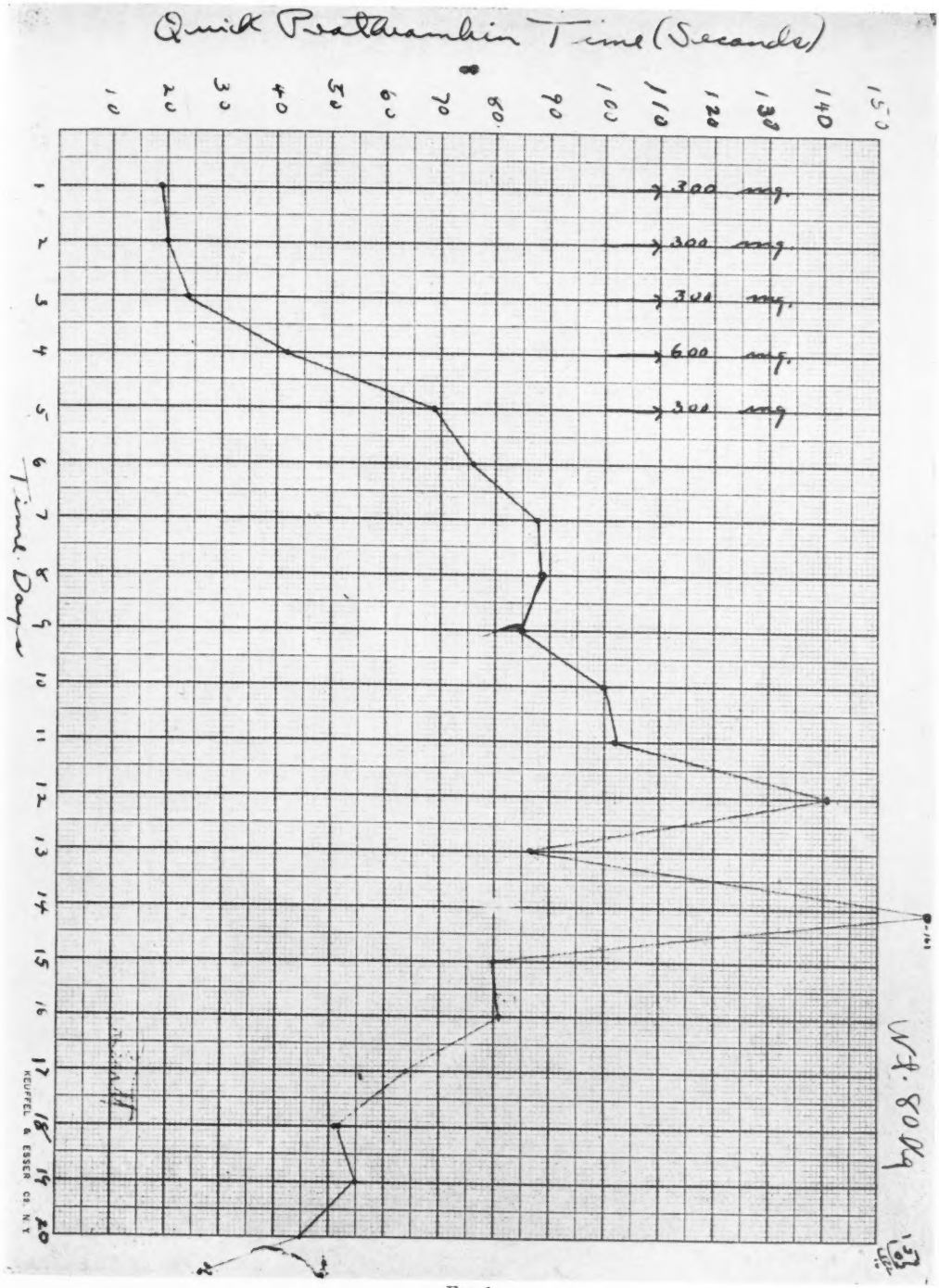
Quick Prothrombin Time (Seconds)
10 20 30 40 50 60 70 80 90 100 110 120 130 140 150
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Time. Days
300 mg.
300 mg.
300 mg.
600 mg.
300 mg
KEUFFEL & ESSER CO. N.Y.

FIG. 1

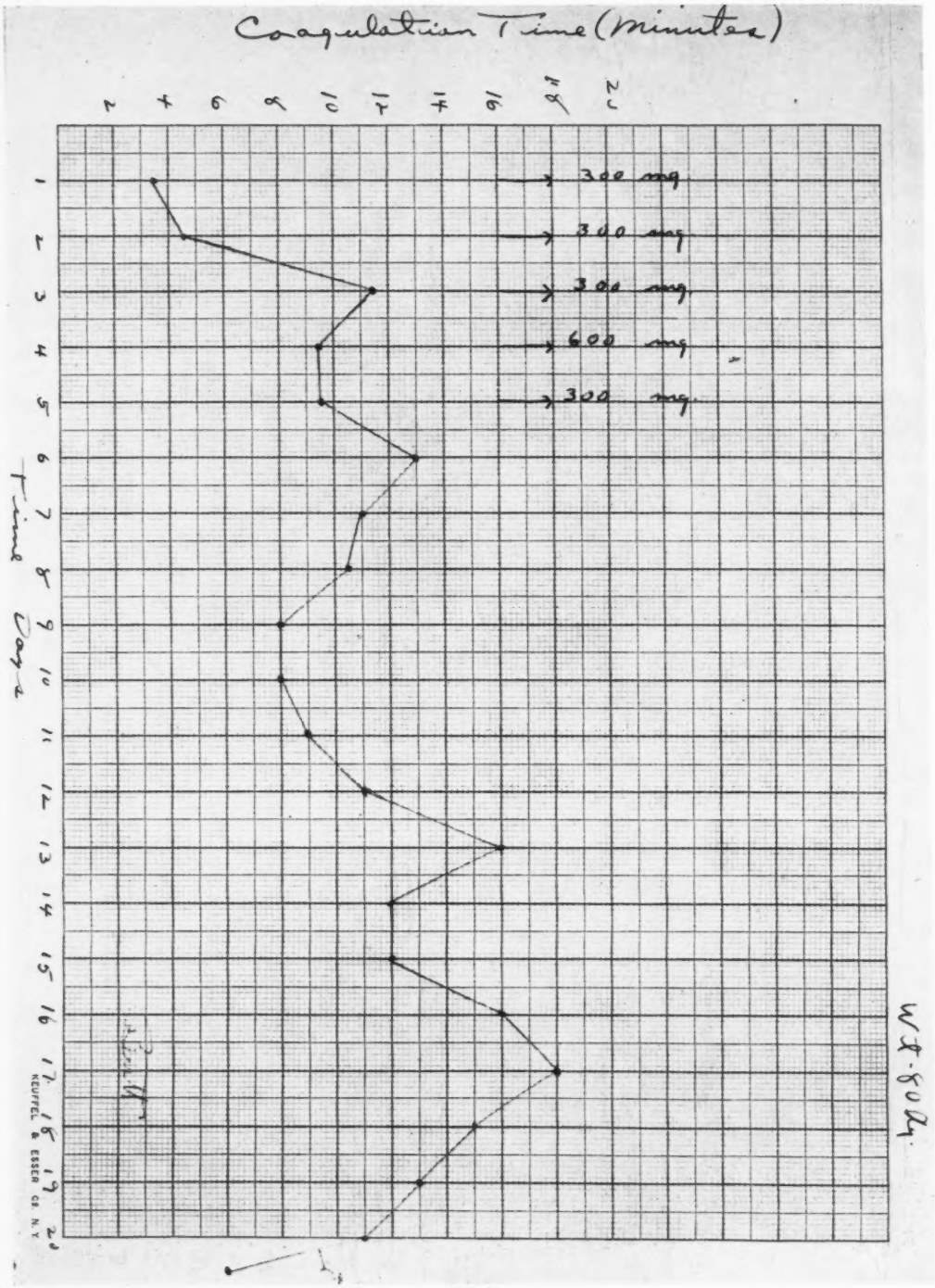
Coagulation Time (minutes)
300 mg.
300 mg.
300 mg.
600 mg.
300 mg.
Time Days
KEUFFEL & ESSER CO. N.Y.
W.T. 600 Mg.

FIG. 2

vitamin K enhance prothrombin activity when deficiency of prothrombin has been induced by the use of Dicumarol, although small doses fail to do so.

We protected our first patient from injury, and within 20 days the prothrombin activity and the coagulation time of the blood had returned to normal (figs. 1 and 2). His health had not been impaired in any way.

At that time Dr. Butt and I believed that we were the first to administer what since became known as Dicumarol to a human being, but Dr. Link said in his Harveian Lecture, delivered on January 20, 1944, that the anticoagulant had been given to the clinical group at the Wisconsin General Hospital, Madison, in September 1940. Dr. Ovid O. Meyer subsequently told me that he and his associates had first given Dicumarol to human patients in December 1940 or in January 1941. However, the first patient received 10 mg. of Dicumarol on the first, third, and fifth days, 25 mg. on the sixth day, and 50 mg. on the tenth day of observation. Eleven additional patients, with one exception, received single doses ranging from 50 to 100 mg. of Dicumarol. Study of the blood of these patients showed that in 5 instances there was prolongation of the prothrombin time from an average control level of 10 seconds to an average maximal level of 12 seconds.

When I was attending the annual meeting of the American Medical Association in 1941 I received a telegram from Dr. Butt relative to some aspect of the problem. Shortly afterward I told Dr. Irving S. Wright, of New York City, that we were carrying out studies that might have great importance. I told him I did not wish to disclose the nature of the studies because they were in a preliminary stage. He replied that he also was anticipating carrying out studies of interest, but declined to give information for the same reason I had declined. It was not until some time later that it was disclosed that both of us had Dicumarol in mind.

In the issue of the *Proceedings of the Staff Meetings of the Mayo Clinic* for June 18, 1941, Dr. Butt, Dr. Bollman, and I published the first report of the administration of Dicumarol to man.

Of this report Dr. Link wrote in his Harveian Lecture, "Boldness, a combination of right talent and an objective point of view . . . enabled them to publish the first preliminary clinical report . . . ," and that "Messrs. Butt and Allen gave it in full therapeutic doses to six human subjects."

The editorial comment on our report in the September 13, 1941, issue of the *Lancet* was given the title, "Heparin and a Rival." On May 4, 1942, the presentations on behalf of the speakers and their associates were by Dr. Irving S. Wright, of New York City, Dr. Ovid O. Meyer, of Madison, Wisconsin, and by myself before the American Society of Clinical Investigation. At the annual meeting of the American Medical Association in June 1942, 3 more detailed presentations were made before the meeting of the Section on Experimental Pharmacology and Therapeutics.

Needless to say, Dicumarol and similar substances have proved of great value in clinical practice; the use of them has saved many lives. The story which I have related, based on my personal participation in it, is the story, "From the Haystack to the Human,"* for treatment of diseases of man with Dicumarol resulted from original studies by Link and his associates on the cause of hemorrhagic disease of cattle which occurred when they ate spoiled sweet-clover hay.

There is another chapter yet to be written. Identical amounts of Dicumarol and substances that have a similar action produce diverse effects on the prothrombin activity of different persons, and on the prothrombin activity of the same person at different times. Hence, an effect that is constant in quality cannot be anticipated accurately. What is urgently needed is a preparation which, when administered in the same amount, always produces the same effect. Such an accomplishment seems improbable and perhaps impossible, but we are bound to remember that in 1939 Dicumarol also was "impossible."

*The designation of a newspaper reporter.

Historical Notes on the Early Development of Anticoagulant Therapy with Dicumarol in Sweden

By JÖRGEN LEHMANN, M.D., PH.D.

THE INTEREST in anticoagulant therapy of thromboembolic diseases was stimulated in Sweden during the years 1935 to 1937 due to the work of Jorpes and co-workers on heparin. The author's participation in this field was facilitated when he was appointed in 1938 as director of a newly erected central laboratory for clinical chemistry in the city hospital of Gothenburg-Sahlgrens Hospital. A new laboratory building, equipped with animal rooms, operating room, etc. for work in experimental medicine, was opened on September 1, 1940. A few days before this celebration, a big truck turned up at the front side of the laboratory building, loaded with hay of sweet clover (*Melilotus albus*) harvested at the dustyard at Hisingen, outside Gothenburg. At the top of this load the assistant doctor of the laboratory, Johan Mårtensson, was seated, and the truck was followed by the author, riding a bicycle. Astonished and wondering laboratory technicians gathered at the windows at this peculiar appearance—this was something unusual.

The hay was brought into a small, closed room of the laboratory and left for spontaneous molding, after which it was fed to rabbits. The aim was to see if the hemorrhagic disease described in cattle by Schofield[1] and Roderick,[2] mentioned in a paper by Quick,[3] could be reproduced. This would be of interest, as the toxic principle in the hay might be extracted and purified for clinical use in thromboembolic diseases. It was suspected to be a derivative of coumarin. This anticipation was based on a personal communication during the summer of 1940 from Dr. Göte Turesson, Professor of Plant Systematics and Genetics at the Royal Agriculture College in Upsala, whom the author had told about the bleeding disease in cattle. Dr. Turesson mentioned the high concentration of coumarin in sweet clover and the efforts in Canada of producing new coumarin strains which might produce a better food for the cattle. We looked up the structural formula of coumarin, and the author was struck by the close relationship between coumarin and naphthoquinone, the essential part of the recently synthesized vitamin K (Fieser[4] and Doisy[5]). This relationship might possibly explain the mechanism by which the toxic principle was active, namely, as a competitive inhibitor of vitamin K, thereby depressing the synthesis of prothrombin in the liver and producing a lowered coagulability of the blood.

The author was familiar with such substrate inhibitions of enzyme activity from many years of work on dehydrogenases in Thunberg's laboratory at the University of Lund, and especially from the work of Quastel and Wheatley[6] on the specific inhibition of the oxidation of succinic acid by the closely related malonic acid.

The relationship between coumarin and vitamin K brought the sweet clover experiments in touch with earlier experiments of the same year (1940) in which preliminary experiments with naphthoquinone as a vitamin K inhibitor had been performed—but in vain.

Other methods of producing inhibition of the coagulation process were then tried (July 1940) with Benzoechtrosa (Kahlson and Landby[7]) but were found to be not applicable in the clinic.

After the visit to Dr. Turesson in Upsala the author's interest was directed toward coumarin. Even before the experiments with molded sweet clover were started, coumarin was tried as an anticoagulant in rabbits, given intramuscularly in doses of 0.15 to 0.20 Gm., dissolved in sesame oil, and 0.5 Gm. dissolved in 6 ml. of 30 to 45 per cent (v/v) ethanol

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nd given by stomach tube. With the last loses definite prolongation of the prothrombin ime, but not of the spontaneous coagulation ime, was achieved (August 15 to 21, 1940). 'hese experiments were considered as unpromsing and given up.

Experiments with spontaneously molded sweet clover hay were begun in rabbits (October 11, 1940). No fully conclusive results were obtained. The experiments were continued in 1941, when the hay was molded with *Asperigillus niger* and *Asperigillus fumigatus*, kindly supplied by Dr. Rennerfeldt at the Botanical Institute of Gothenburg and known to be active in producing the "toxic" substance. On March 23, 1941, a successful series of experiments was started, succeeded by preliminary extraction experiments. However, the papers of Dr. K. P. Link and his coworkers[8–11] on the isolation and synthesis of the active principle in spoiled sweet clover hay appeared in the Journal of Biological Chemistry, and these experiments were therefore stopped (May 1941).

A new epoch opened for us when 3,3′-methylene-bis (4-hydroxy-coumarin) was synthesized by Mr. Rosdal at the Ferrosan Company, Malmö, Sweden. The first sample was received on June 26, 1941. Animal experiments began on June 30 in 13 rabbits and a few dogs and were finished on August 14. The reversibility of the prolongation of the prothrombin time and coagulation time was demonstrated. No liver injury could be demonstrated by microscopic examination even after long-term treatment of the animals. The antagonistic effect of blood transfusion was shown. Synthetic vitamin K was also tried in a dose of 5 mg. to a rabbit but did not inhibit the effect of Dicumarol (July 12, 1941). This was a great disappointment, as the anticipated competitive inhibition of vitamin K was thereby questioned. However, later in a critical situation with an oozing bleeding from the intestinal mucosa of the anus in a young woman, 200 mg. of vitamin K (2-methyl-1,4-naphthohydroquinone disulfate) was given with immediate effect (Jan. 5, 1942, Surg. Dep. II, Jl.Nr 3347/41).

When the animal experiments were finished, the author was very much in doubt if they should be published at once. In spite of the fact that they were promising as an anticoagulant treatment for thrombotic diseases, which was the aim of the experiments, it was decided not to publish any experiments before the effect had been demonstrated in patients suffering from thromboembolic disease. The main argument for this decision was the critical attitude which clinicians in Scandinavia often had shown against animal experiments as a guide to human therapy. Premature conclusions would presumably hurt the future development of the experiments. The author was even cautious in keeping the experiments secret within the laboratory as well as within the hospital. In the animal protocols Dicumarol was signed as "X-substance."

The details of the early clinical use of Dicumarol in Gothenburg have been published elsewhere.[12–16] The care of the patients with thrombosis during the first years was assigned to the author, who is especially grateful to Dr. Gustaf Pettersson, Surgical Department II, the first doctor in the hospital to whom the Dicumarol experiments were mentioned, and whose patients were the first to be treated. (The first patient suffering from thrombosis was treated on October 11, 1941. Surg. Dep. II, Jl.Nr 2619/41.)

After the first presentation of the clinical results November 29, 1941, in Stockholm (published in *Svenska Läkartidningen*, January 9, 1942), the author was confronted with the problem of how to get a paper published in the international literature. All regular communications with England and America had stopped because of the war. The only communications with England were irregular and by planes during the night. These were often heavily attacked by German planes. However, the British Consul General in Gothenburg was kind enough to take care of a paper for *Lancet* (December 23, 1941).

Nothing was learned about the fate of the paper until a letter arrived from Dr. Link,

dated April 20, 1942. With Dr. Link's permission the letter is here published.

Dear Dr. Lehmann,

I was very glad to see your account in the Lancet entitled Hypo-prothrombinaemia produced by Methylene-Bis-(Hydroxycoumarin) 3/14/42.

It is clear from this excellent and highly condensed note that you have made very substantial progress toward evaluating the possible therapeutic potentialities of the substance. I would be very glad to have reprints of your work as it appears.

By separate post I am sending you reprints of our work which has appeared in print to date. The following papers are in press:

VIII. The effect of 2-Mthyl-1,4-Naphthaquinone and l-ascorbic acid upon the action of 3,3′-methylene-bis (4-hydroxycoumarin) on the Prothrombin Time of Rabbits. Jour. Biol. Chem.

IX. The effect of diet and Vitamin K on the Hypoprothrombinaemia induced by 3,3′-methylene-bis (4-hydroxycoumarin) in the rat.

A critical study on the role of l-ascorbic acid in the rat and guinea pig in so far as it affects the dicoumarin has been completed and will be ready shortly.

We were very much impressed by the fact that your reasoning on the action of l-ascorbic acid and the possible antagonistic action of vitamin K paralleled our thinking. Furthermore I think in figure 1 of paper VII and the first figure in your Lancet article bear a striking parallelism.

With best wishes and kindest regards,

Karl Paul Link

None of the papers from Dr. Link was ever received. From the author's answer to Dr. Link, dated July 13, 1942, the following is quoted.

Dear Dr. Link,

Very many thanks for your kind letter of 4/20/42, which I received 6/25/42. It was the first announcement to me, that my paper had been printed in the Lancet. I sent it to the editor 12/23/41 and have not heard anything about the fate of the paper until I received your letter. We have only air mail connection with England and the sendings are therefore very restricted. We can't get the Lancet here in Sweden. Therefore, Dr. Link, your letter was especially welcome. I have now asked the editor for a few reprints and I will send you one as soon as I have got it. It contained a summary of my other papers, which are written in Swedish. It will be of great interest to me to read the papers mentioned in your letter. They have not arrived yet.

An attempt was even made in April 1942 to have a paper published in *Science* in the U.S.A. as elucidated from the following letter to a friend of the author, Dr. Frederick Bernheim, Duke University School of Medicine.

Göteborg, April 11th, 1941.

Dear Frederick,

A friend of mine, captain on a Swedish boat,* has promised me to forward this letter to you, when coming to your continent. I enclose parts of a paper, which I think will be of interest for you. When I had finished the paper in 1941 I had written a summary for Science, but just as I was going to send it, the post for U.S.A. was stopped. If it is possible I should be glad if you would forward it to Science. For such a case, please correct it and make a choice of the figures. I am sorry not to be able to send the figures to paper 2 (in print), but I think it can be printed without the figures. I have heard of a friend of mine, that some doctors at the Mayo clinic (H. R. Butt, E. V. Allen a. J. L. Bollman) have been working on the same subject. Would you kindly send them paper II when having used it for Science. I send them the summary of paper I. (They are working at the Mayo clinic, Rochester, Minn.)

Even the fate of this paper was unknown to the author for about a year. From a letter to Dr. Bernheim February 28, 1943, it is evident how the author received information about its publication October 9, 1942.

Dear Frederick,

Very many thanks for your letter of November 3, 1942, which I received February 26, 1943. For a week ago I heard from the Swedish-American News Information in Stockholm that a paper of mine in Science had been mentioned in Science News Letter and from that I understood that you had got my letter and been kind to send a note about it to Science. I am awfull glad for your kindness.

The poor communication between Gothenburg and U.S.A. during the war is shown by

*The boat *Svealarl* was torpedoed on the next sailing, and the captain and most of the crew were drowned.

the following letter, dated June 1, 1943, to Dr. Bernheim.

Dear Frederick,

. . . Further I should be glad to know if any papers have appeared in U.S.A. on the use of the dicoumarin in thromboembolic diseases and their results. In the Lancet May 15, 1943 my clinical results for 1942 have been published. The dicoumarin is now in use in many hospitals in Sweden and so far I know with good results.

The last phase in the development of the use of Dicumarol was the treatment of coronary infarction. The first case, complicated with a thrombosis antecruris, was treated November 7, 1941, (Dep. Vasa. . . . Julia M-g, admitted November 2, 1941). On proposal of, and in cooperation with, Dr. Bo Ewert, Medical Department I, a more consistent but cautious treatment of selected cases was started in 1942. Of 47 cases, 16 were treated with 0 per cent mortality as compared with 45.1 per cent of the untreated group. During 1943 the corresponding figures were 31, of which 16 were treated, with 25 per cent mortality as compared with 64.2 per cent in the untreated group. During 1944, 57 cases were treated of a total of 76, with 25.9 per cent mortality as compared with 47.3 in the untreated group, and in 1945 (January 1 to June 30) 43 out of 46 were treated, with a mortality of 20.9 per cent. Since then nearly all cases have been treated with Dicumarol, often combined with heparin. (The figures mentioned above have been compiled by Dr. Albert Larsson, and read before the Swedish Society for Internal Medicine, September 8, 1945, but this paper has as yet not been published.)[17]

After 1945 the treatment of thromboembolic patients as well as of patients with coronary infarction in Sahlgrens Hospital was taken over by the physicians of the different departments. In many hospitals in Sweden Dicumarol was then in use. Especially at the University clinic in Lund a careful study was made of the prophylactic and curative use of Dicumarol in surgical patients.[18]

This review of the early events in the use of Dicumarol in Sweden can best be finished by quoting a letter from the author to Dr. Link dated June 13, 1942.

It was surprising but a striking fact, that the year 1941 was mature for a more detailed study of the toxic agent in sweet clover hay as it was studied at the same time in your laboratory and here. I have now treated nearly 200 patients with the dicoumarin and the results are even as good as those from patients treated with heparin.

I hope I will be able to meet you once in the future, when the world has found itself again. I was working 14 months 1935-1936 in the Rockefeller Institute in New York (Neuro-physiology by Dr. Gasser) where I spent some of the most interesting time in my life and I do hope I will get time for another trip to U.S.A.

With kindest regards,

Sincerely yours,

Jörgen Lehmann

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Post-Thrombotic Sequelae Preventable with Anticoagulant Therapy

By HARRY ZILLIACUS, M.D.

AFTER FIVE YEARS of duty as a military physician in the war, I felt a strong urge to carry on some research investigation. As conditions for this were very poor in Finland at that time, I left for Stockholm, where my former teacher of physiology, Prof. R. Granit, working at the Karolinska Institutet, did me the great favor of introducing me to Prof. Erik Jorpes in December 1944. By that time Professor Jorpes was well along in the development of the concept that thromboembolism could be controlled in large measure by the use of anticoagulants. Favorable results for prophylaxis and treatment with heparin had been reported in Sweden by Jorpes, Crafoord, Watterdal, Bauer, Simon, Suve, and Linde. On the other side of the Atlantic encouraging results were reported by Best, Murray, and McKenzie. Similar advantages had been reported following the use of Dicumarol by Wright, Prandoni, Meyer, Allen, Barker, Nygaard, Walters, Priestly, Waugh, Butsch, and Stewart, in the United States, and by Lehmann and Bruzelius in Sweden.

In 1945, Bauer, reporting a series of 103 patients, drew attention to the possibility of preventing post-thrombotic sequelae by treating the very early stages of deep venous thrombosis with heparin. As these observations were based on relatively few patients there remained some doubt about the specificity and effectiveness of the anticoagulants. I felt, therefore, very fortunate to be asked by Professor Jorpes to organize a study, based on a large number of patients, to evaluate anticoagulant therapy in the control of acute deep vein thrombosis and reduction of the risk of pulmonary emboli and other post-thrombotic sequelae. Through the courtesy of the Chiefs of Staff of 15 leading hospitals in Sweden and 2 in Finland it was possible to review the material on 1,158 cases of deep thrombosis of the veins of the legs. This report was published under the title, "On the specific treatment of thrombosis and pulmonary embolism with anticoagulants, with particular reference to the post-thrombotic sequelae" (*Supplementum Acta Medica Scandinavia*, 1946). It was found that specific therapy with anticoagulants shortened the time the patient had to stay in bed to about one fifth of that required by conservative therapy. The thrombotic process could usually be limited to the vein in which it was first diagnosed. It was also established that under anticoagulant therapy the frequency of pulmonary embolism in thrombotic cases decreased from approximately 30 to 0.5 per cent, and that the earlier high mortality from this much dreaded complication was reduced to almost nil. In the course of follow-up examinations of 609 patients who had suffered from an acute deep venous thrombosis from 1 to 5 years previously, it was found that post-thrombotic sequelae, including chronic edema, induration, eczema, pain, and leg ulcer, occurred in 4 out of 5 patients conservatively treated. In those patients in whom early diagnosis was still limited to the calf, and anticoagulants were administered, post-thrombotic symptoms were mostly absent or very mild. One decade later, in 1946, Gjöres (Acta Chirurgica Scandinavia, Suppl. 206) found in a follow-up study of 303 patients an incidence of post-thrombotic sequelae very similar to the corresponding figures in my investigation.

In the discussion of my thesis I had stressed that thrombosis, probably due to anatomic reasons, was found much more frequently in the left than in the right leg, and that this was reflected in the more frequent occurrence of post-thrombotic sequelae in the left leg. I

From the University Hospital for Women, Helsinki, Finland.

had pointed out that this correlation could be confirmed by watching ladies legs in the street, and soon thereafter I received a telegram in which congratulations were sent by The Society for Saving the Beauty of Ladies' Legs. I have always suspected that this originated from Professor Jorpes!

The great number of thrombotic cases examined in the course of this investigation established the fact that anticoagulant therapy for thromboembolism was about as specific as insulin therapy for diabetes. The evidence clearly demonstrated that with the aid of anticoagulants thrombosis could be controlled in the acute stage, and post-thrombotic sequelae thus avoided. My additional studies in this field are found in the reference list of this article.

This early experience with the problems of coagulation and thrombosis has been of the greatest value in the prevention and treatment of thrombosis on my obstetrical service, where 5 000 obstetrical and 1,000 gynecological patients enter the I. University Hospital fo Women in Helsinki annually.

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Personal Experiences with Anticoagulants for Coronary Atherosclerosis

By E. STERLING NICHOL, M.D.

CLINICAL REPORTS about Dicumarol in 1941 by Meyer, Bingham, and Pohle (Madison), Butt, Allen, and Bollman (Rochester) aroused my interest, which was further whetted in October 1941, by Wright and Pranloni's lecture at the New York Academy of Medicine. These authors discussed the use of Dicumarol in venous thrombosis, pulmonary embolism, rheumatic heart disease, and peripheral arteriopathies. During 1942 at various times I talked about the possibility of utilizing Dicumarol in acute coronary thrombosis with myocardial infarction with Nelson Barker, Wilbur Duryee, Irving Wright, and others. Considerable doubt was expressed as to the likely results, but it was agreed that a clinical trial would be worthwhile. About this time, Clarence de la Chappelle noted an incidence of 12 per cent thromboembolism following acute infarction and stated, "Some day it may be demonstrated that [mural thrombi] will be prevented by the use of an anticoagulant such as heparin or dicoumarin." In June 1943, after hundreds of patients with thromboembolism had been treated with Dicumarol by various workers, I gave Dicumarol to my first patient with acute coronary thrombosis. After this initial venture, I continued to use Dicumarol routinely in acute myocardial infarction. No data on the use of Dicumarol in acute coronary thrombosis were available, but Barker had told me of its trial in a few cases, and after my study began, Wright and Duryee informed me that they had successfully used Dicumarol in 9 cases of coronary thrombosis. During 1944, casual references to the use of Dicumarol in acute coronary thrombosis appeared in papers describing its *general* use, Lam listing 3 cases, Evans 1 case, Gefter et al. 1 fatality, Townshend and Honingman 3 cases, and LeFevre mentioned 7 cases in 1945.

In October 1944 I reported the results of Dicumarol therapy in 30 patients with "acute coronary thrombosis" at a meeting of the Miami Heart Association (I keep these lantern slides for sentimental reasons). I was naive enough to believe, since the patients did well, the discussion would arouse interest in what seemed a truly constructive advance in the treatment of acute myocardial infarction, but instead of approbation, asides were audible anent my cerebral "slip" showing! In spite of the prevailing opinion that such therapy was meddling and dangerous, within another year I compiled the data obtained in 50 acute attacks, but this manuscript was returned with a frank note that it lacked scientific basis by the Journal of the American Medical Association. In my "President's Address," American Therapeutic Society, November 11, 1945, I related the results of my study. My closing remarks were, "Dicumarol is not the ideal therapy for coronary artery thrombosis, but it is a step forward. Two patients had each experienced three episodes of coronary thrombosis within two years, so were given Dicumarol continuously for 1 year as a protective measure, watching the prothrombin time at intervals. It may be more than coincidence they have not experienced a fourth attack. I look forward with confidence to the development of more easily controlled drugs to prevent intravascular thrombosis—or is this a fond dream of a middle-aging physician desirous of eluding the onslaught of time?" My data were buried in the Society Transactions and overlooked by other workers. The report was published* in full in January 1946. Because of similar studies by Wright, Peters, et al., the American Heart Association sponsored in 1946 an investigation of the values of anticoagulants in myocardial infarction. A debt of gratitude is owed to Irving Wright, Charles Marple, and Dorothy Beck for their hard work in correlating the data furnished

*My former associate, Dr. Samuel Page, co-author.

by 16 investigators. Parker and Barker reported good results in acute coronary thrombosis soon, and a flood of similar papers appeared. In 1949 editorials appeared in several leading medical journals anent the use of anticoagulants in acute myocardial infarction. From June 1943 to June 1953 my associates and I treated 207 patients suffering acute myocardial infarction with anticoagulants. The over-all mortality rate was 14.3 per cent. (A 6 week interval was considered as the acute stage instead of the 4 week interval used by some authors.)

Twenty-two autopsies (71 per cent) were obtained. Rupture of the ventricle was found in only 3 cases (1.3 per cent), which suggested that the size of the infarcted area was limited in extent by energetic anticoagulant therapy. In contrast, Waldron found 15 per cent of 71 cases treated with anticoagulants developed myocardial rupture and 4.9 per cent of 241 patients *not* treated with anticoagulants. Mural thrombi were found in only 2 cases. We rarely encountered "pericarditis epistenocardica" in patients who were fully heparinized early.

Armand Quick's 1-stage method of prothrombin determination soon became established as a guide in adjusting the Dicumarol dosage. In 1943 Miami was not overflowing with competent laboratory technicians so it devolved on me to learn the pitfalls of prothrombin tests to make sure that technicians performed such tests accurately. During this early period I admitted a woman with an acute attack to a hospital where the laboratory declined to set up a prothrombin method on the grounds it would seldom be used! Harrowing experiences with prothrombin tests done in outlying towns led to not a few acrimonious remarks about Dicumarol therapy, but eventually all hospitals and private laboratories in the area instituted the needed coagulation methods.

Most workers at first transposed the results of the prothrombin time to a hyperbolic serial dilution curve and expressed results in "percentage of prothrombin activity" rather than in "seconds of prothrombin time." Study of the pitfalls in computing "percentage" of prothrombin activity convinced me that maintaining the prothrombin time between 2 and 2½ times the normal would provide a satisfactory range of hypoprothrombinemia, and I urged an early Anticoagulant Panel of the American Heart Association to report prothrombin tests in "seconds" instead of "percentage." Shepard Shapiro stated in 1951, "The clinician should know the normal range of the thromboplastin used and the therapeutic range he wishes to establish in terms of time. With this knowledge the calculation of percentage is superflous; without it, the percentage figure is misleading." Some laboratories here and abroad computed a "percentage of prothrombin" or "clotting index" by a linear ratio of the normal prothrombin time compared to the patient's prothrombin time, which led to gross errors in adjusting Dicumarol therapy. The Link-Shapiro modification of Quick's method, comparison of the prothrombin time of a 12.5 per cent plasma dilution with that of whole plasma, has some advantages. Although the 2-stage prothrombin method is often advocated, in our hands it has not been of superior value in regulating anticoagulant dosage. In 1945, Hurn, Barker, and Magath pointed out that the nature of the thromboplastin used has great bearing on the validity of the prothrombin tests, and marked discrepancies arising from various thromboplastins employed were emphasized by Bramble. Knowledge about the vagaries of prothrombin tests has not become widely disseminated. Our laboratory ran thousands of tests between 1945 and 1955 using 2 different sources for thromboplastin (rabbit lung and brain) and the conflicting results with "pathologic" plasma were often so striking that repeated studies sometimes uncovered a hidden source of error, but more often the variation was due to the difference in the source of thromboplastins. Recently variable results obtained using different thromboplastins were carefully analyzed in an excellent exposé by Verstraete, Clark, and Wright.

When Moloney in 1948 showed the effect of Dicumarol on the clotting time in silicone-

treated tubes, I meticulously prepared such tubes, only to find that clotting was often delayed several hours, so I abandoned this procedure as impractical.

Heparin

Jay McLean, studying the blood clotting effect of cephalin, incidentally discovered the anticoagulant heparin in 1916; hence the finding of this natural anticoagulant as well as Dicumarol may properly be termed "serendipitous." McLean's recent obituary in the Journal of the American Medical Association made no mention of heparin, one part of which will prevent the clotting of 100,000 times its weight of blood! In 1936 heparin was purified sufficiently by Charles and Scott to permit its clinical trial in thromboembolism. On the basis of animal experimentation, Best suggested in 1940 that heparin might prove effective in the treatment of acute coronary thrombosis, but it was seldom utilized during the next few years. Only after McLean's talk in 1945 I began to use it, and have relied on it more and more during the initial 7 to 10 days of the acute episode.

Helen Glueck and co-workers in Cincinnati reported on the combined use of heparin and Dicumarol in myocardial infarction in 1948. About the same time Loewe reported on the use of heparin* alone during the acute and healing stage of myocardial infarction. In 1949 I treated 24 patients with acute coronary thrombosis for 4 to 6 weeks with delayed action heparin† with good results except for occasional painful hematomas, but I failed to report my experience. Since the description by Stats and Newhof in 1947 of the advantages of concentrated heparin, I have used this preparation, preferably in concentration of 200 mg. per ml. The dosage ranges from 50 to 75 mg. every 6 hours, given subcutaneously not intramuscularly, in the areolar tissue along the iliac crest. Heparin tolerance tests and heparin-retarded coagulation times as indicators of the need for heparin therapy proved unreliable. I found no occasion to use hyaluronidase with depot injections to minimize pain as suggested by Tuchman and Moolten. In spite of the fact that heparin induced bleeding sometimes, protamine sulfate was required to control bleeding in only 1 patient. The prolongation of the prothrombin time by heparin as first shown in 1946 by Long and Barker was sometimes a source of dosage error when changing from heparin to other anticoagulants, until we became more alert.

*Heparin in Pitkin-Menstruum, Warner Company.
†Depo-hepin, Upjohn Company.

Long-Term Therapy in Coronary Disease

In February 1944 I began long-term anticoagulant therapy to forestall recurrent myocardial infarction, and made a preliminary report* before the Southern Medical Association in November 1946. Although Wright and Foley had begun continuous treatment in rheumatic heart disease with embolic episodes, no trial of long-term anticoagulant therapy to prevent myocardial infarction had been essayed. The first patient treated merits some description.

Patient J.R.T., aged 54 years, had an attack of posterior wall myocardial infarction in January 1943. Six months later, he had a severe anterior infarction and was treated with Dicumarol for 6 weeks. In February 1944, he developed a third attack. Dicumarol therapy was instituted again and this time was continued to see if additional attacks could be warded off. In December 1945, gross hematuria with renal colic appeared, but never recurred. In November 1946, hematemesis and tarry stools developed due to a bleeding peptic ulcer. Dicumarol was omitted for 5 weeks, then resumed because of worsening anginal pain. Attacks of bronchitis recurred frequently and pulmonary emphysema developed in 1948. The Dicumarol requirement was remarkably constant (700 to 800 mg. weekly) until a summer holiday in 1948 in Nova Scotia when he imbibed ale instead of milk, a dietary change which reduced his Dicumarol requirement to 600 mg. weekly. He continued business activities up to 6 months before his death, when he gradually developed intractable congestive heart failure, azotemia, and anemia. As inanition increased, his Dicumarol requirement dropped to 500 mg. per week. He was comatose for 3 days before death. Continuous Dicumarol therapy had been followed for 90 months, except

*My associate, David Fassett, was co-author.

for 5 weeks during the bleeding ulcer episode. Autopsy showed no fresh coronary thrombus or infarction, old posterior wall infarction, calcified left ventricular aneurysm, nephrosclerosis, purulent bronchiolitis and emphysema, and healed gastric ulcer.

It would be an understatement to say it was an uphill battle, promoting the concept that permanent ambulatory anticoagulant therapy was feasible and worthwhile. In spite of the askant mien of my colleagues, I took heart in reading again a statement first made by E. V. Allen in 1945, "It is timely to consider that blood may normally clot in blood vessels *too well* to serve the interest of the health of man —some time in the future there may be no valid reason why the coagulability of the blood in man may not be maintained indefinitely and safely at a level which will not permit intravascular thrombosis." In 1949 Foley and Wright reported their results in 19 patients on long-term therapy, 5 of whom were "coronary" patients. Yet Bean in the same year stated that the use of anticoagulants in ambulatory patients as a prophylactic measure was out of the question! In 1950, Borg and I reported on 78 patients treated continuously to prevent recurrent myocardial infarction. Subsequent reports by Hellem, Keyes and co-workers, Suzman and co-workers, Owren, Coogan, and Davis, Tulloch and Wright, Manchester, and more recently Bjerkelund and Owren, indicated benefit from permanent anticoagulant therapy. A cooperative study comprising 1,091 cases treated by 10 physicians* for a total of 24,454 months, compiled by me in 1954, but only published recently, confirms the value of long-term anticoagulants in reducing the incidence of recurrent myocardial infarction and in lengthening the span of life after 1 or more attacks.

Impending Myocardial Infarction

During long-term anticoagulant therapy to prevent myocardial infarction, it appeared likely that some episodes of worsening anginal pain might well have ended in full-blown myocardial infarction had anticoagulants not been in force. This observation led me in 1946 to use anticoagulants in patients presumed to be showing premonitory signs of myocardial infarction, a condition which at the outset is indistinguishable from the clinical syndrome of acute coronary insufficiency since the eventual diagnosis is made only in retrospect after a number of days have elapsed. Results in 41 patients in this category constituted my "Address of Chairman," Section of Medicine, Southern Medical Association, November 1949, published in July 1950, and was the first paper on this topic in the world literature. Paul Wood had described the use of anticoagulants in 10 cases of "angina at rest" at the December 1948 meeting of the Medical Society of London. In April 1954 I reported results obtained in 150 additional cases at the American College of Physicians. My associates and I during the past 11 years have treated 313 private patients presenting premonitory signs of myocardial infarction, heparin being used for 1 week before instituting oral anticoagulants. Relief of pain was often strikingly coincident with full heparinization. Only 20 of the 313 patients (6.3 per cent) developed frank myocardial infarction, 5 of whom died within 30 days. Of the remaining 293 cases not developing frank infarction, none died within 60 days while using anticoagulants. Twenty-seven patients abandoned anticoagulants before the expiration of 60 days, of whom 16 (60 per cent) developed frank infarction during the ensuing 60 days. (Unpublished data except for an abstract in the program of the 1957 American Heart Association Clinical Sessions) Similar observations have been reported since 1952 by Maynard, Thompson, Engelberg, Lenègre, and Beaumont, and in the past year by VanderVeer, Anderson, and Waaler.

Notes on the Risk of Hemorrhage

Clinical bleeding due to anticoagulants was first described by Prandoni and Wright in 1941, and by the year 1948, 28 deaths were recorded in the world literature ascribed to the use of anticoagulants, at which point I

*Co-authors: John N. Keyes, Joseph F. Borg, Thomas J. Coogan, John J. Boehrer, William L. Mullins, Thornton Scott, Robert Page, George C. Griffith, Edward Massie.

btained by questionnaire further data from 36 clinicians who reported that significant emorrhage occurred in 2 per cent of 15,500 atients *with 35 deaths not previously reported.* My paper on "Risk of Hemorrhage" ppeared in February 1950 and was later summarized as a guest editorial in the J.A.M.A.)ne instance of hemopericardium without nyocardial rupture due to anticoagulant therapy in acute myocardial infarction was included, but the first case report dealing with his complication was made by Hammarsten in 1949 and was further emphasized by Goldstein and Wolff in 1951. Three deaths resulted primarily from performing lumbar sympathetic blocks when anticoagulant effect was in force, although hemorrhage was found elsewhere in these cases. The concomitant use of heparin and spinal anesthesia in 1 case, causing transverse hemorrhagic myelitis, and the performance of dorsolumbar sympathectomy without omission of anticoagulants in another, accounted for 2 deaths, both deaths exemplifying poor clinical judgment rather than faulty anticoagulation measures. Most instances of major bleeding were associated with pathologic lesions. The first case of vaginal bleeding in my experience occurred in an elderly woman being treated for coronary thrombosis who proved to have an early carcinoma of the cervix. Sometimes melena induced by anticoagulants led to the discovery of an occult lesion in the gastrointestinal tract.

An extraordinary hemorrhagic death* was hat of a 53 year old man on long-term therpy to prevent recurrent infarction, who deeloped a peritonsillar abscess complicated by dema and hemorrhage into the cervical structures and larynx which produced fatal espiratory obstruction while he was en route o a hospital by ambulance. (Death might ell have been prevented by earlier hospitalzation.)

Although hematuria was the most common ype of bleeding encountered, in no instance as it fatal or followed by added renal imairment. Ureteral colic from clots may follow the free use of vitamin K-1 in hematuria as first noted by me in 1945. One death due to hemorrhage from dissecting aortic aneurysm mistakenly treated as pulmonary infarction was reported by Evans in 1944 and I recorded 2 examples, one wrongly diagnosed as myocardial infarction, the other as saddle embolus. The incidence of fatal hemorrhage in the cooperative long-term study was 0.5 per cent in 1091 patients treated for an average of 22.4 months. Permanent use of anticoagulants is naturally associated with a greater risk of bleeding than when anticoagulants are used for a few weeks only.

In 1950 a patient to whom I had administered long-term Dicumarol therapy to prevent myocardial infarction for 6 months became psychotic and attempted suicide by slashing his wrists, so anticoagulants were stopped. He died a few years later with a recurrent infarction. A suicidal attempt by the self administration of sodium warfarin was recorded in 1952 by Holmes and Love.

In March 1954 I wrote:

> Most hemorrhagic episodes developed because of hypoprothrombinemia, but in some instances in patients using Cumopyran the prothrombin time was found well within the accepted safe therapeutic range, but the Lee-White coagulation time was abnormally prolonged, suggesting that in long-range anticoagulant therapy other coagulation factors may be upset.

In 1957 Herbert Sise and co-workers showed that phenylindanedione produces a deficiency of proconvertin factor (factor VII) and plasma thromboplastin component (PTC), thus accounting for some clinical hemorrhagic episodes in the absence of marked prothrombin deficiency. Currently an intensive study of these effects is going on in the Miami Heart Institute Anticoagulant Laboratory under the direction of Paul Boyles in patients on long-term therapy.

Side Effects of Anticoagulants

Alopecia as a toxic manifestation of dicoumarin anticoagulants seems more prevalent in Europe than in this country, and I have encountered only 2 examples, but alopecia induced by heparin is somewhat more frequent.

*Related by Dr. R. V. Edwards.

Lack of toxic effects on the liver due to Dicumarol were reported by Meitus and Wasserman in 1953. Liver function studies and autopsy data from our patients on permanent therapy with oral anticoagulants revealed no hepatic injury.

One untoward effect of oral anticoagulants is the production of fatigue, malaise, or even anorexia in some patients. Skin eruptions, occasionally scarletiniform, may occur. Febrile reactions are not common but one of my patients, whom I attempted to treat continuously, developed a fever in 1950 proven to be due to Dicumarol, and in the next year, during a trial of Tromexan, fever recurred and did not abate till the drug was stopped, but she was able to tolerate Hedulin. The same patient developed moderate alopecia. A colleague, Dr. Sidney Davidson, in West Palm Beach, had the reverse experience with a patient manifesting febrile reaction proved to be due to Hedulin but Dicumarol was well borne.

Heparin intravenously may induce shock-like reactions in "sensitive" subjects, as happened in one of my patients, and a few instances have followed its use intramuscularly. Local reactions at the site of injection of heparin are usually not of consequence.

ABSTRACTS

ATHEROSCLEROSIS

Kokatnur, M., Rand, N. T., and Kummerow, F. A.: Effect of the Energy to Protein Ration on Serum and Carcass Cholesterol Levels in Chicks. Circulation Research **6**: 424 (July), 1958.

The energy to protein (E/P) ratio of the diet had a significant effect on serum cholesterol levels of rats. Corn oil in the diet was found to depress serum cholesterol levels in diets of high E/P ratio but not in diets of low ratios. A low ratio depressed serum levels regardless of the type of fat in the diet. It is suggested that the E/P ratio may represent the unknown factor in the equation of workers who have tried to relate the effects of dietary fats to serum cholesterol levels.

AVIADO

CONGENITAL ANOMALIES

Steinberg, I.: Congenital Absence of a Main Branch of the Pulmonary Artery. Report of Three New Cases Associated Respectively with Bronchiectasis, Atrial Septal Defect and Eisenmenger's Complex. Am. J. Med. **24**: 559 (April), 1958.

Three cases of congenital absence of a main branch of the pulmonary artery are added to the [illegible] cases recorded in the literature. In 1 patient, it was associated with cystic bronchiectasis of the same lung. In the second, an atrial septal defect was associated with absence of the left pulmonary artery. In the third, absence of the right pulmonary artery was associated with the Eisenmenger complex and a right pulmonary artery arising from the ascending aorta. When this anomaly was unassociated with bronchiectasis or intracardiac defects, the patient was usually asymptomatic. Typically, there was a lag in expansion and diminution of breath sounds in the lung with the absent pulmonary artery. Roentgenogram revealed this lung to be small with fine vascular markings, whereas the opposite lung was overdistended and well vascularized, and displaced the mediastinum. Angiocardiography was diagnostic. With bronchiectasis, there may be further pulmonary parenchymal disease leading to cough and a finding of rales. Diagnosis of absence of pulmonary artery when there are septal shunts is more difficult. Such patients are often ill with recurrent infections, dyspnea, and cyanosis. Conventional x-ray helps little; angiocardiography is diagnostic. Cardiac catheterization may be needed to localize the shunt. Differentiation of the isolated type from the complicated type is significant because of therapeutic and prognostic implications.

KURLAND

Davidsen, H. G.: Atrial Septal Defect in a Mother and Her Children. Acta med. Scandinav. **6**: 447, 1958.

This report deals with the unusual occurrence of atrial septal defect in a mother and 2 of her children. A third child had died of congenital heart disease—probably also atrial septal defect. The diagnosis in each of the patients was established by cardiac catheterization and was confirmed in 1 by an operation to close the defect. There is also a review of the literature dealing with the incidence of familial occurrence of congenital heart disease and the reports of families in which 2 or more instances of identical congeni-

tal heart disease had been present. The author believes that modern diagnostic methods that permit more accurate diagnosis and the routine registration of the family histories of patients with congenital heart disease will provide more adequate material for the study of the hereditary factor in congenital heart disease.

BROTHERS

Davidsen, H. G., Fabricius, J., and Husfeldt, E.: Five Cases of Congenital Aneurysm of the Aortic Sinuses (of Valsalva) and Notes on the Prognosis. Acta med. Scandinav. **6:** 455, 1958.

The case records of 5 patients with congenital aneurysm of the aortic sinuses are presented in detail. Cardiac catheterization and thoracic aortography were performed on each patient. The latter procedure was of particular diagnostic value. Two patients had a communication from the aorta into the right heart. One of these had lived for 7 years without progression of symptoms. The other had symptoms of rapidly increasing right heart failure and died during attempted surgical intervention. Two other patients had regurgitation into the left ventricle with a hemodynamic picture resembling aortic incompetence. The fifth patient had no demonstrable abnormality of the circulation and only moderate symptoms. A review of the literature to determine the cause of death in congenital aneurysm of the aortic sinuses disclosed that death can be caused by rupture into 1 of the heart chambers, by compression of the bundle of His, by impairment of aortic valvular function, and by bacterial endocarditis. At the present time, the authors think that surgical repair of aneurysms of the sinuses of Valsalva should be considered only in the small group of patients in whom an aneurysm has ruptured into the right atrium, provided a considerable left-to-right shunt is present, there are no signs of a complicating interventricular septal defect, and there is no endocarditis, syphilis, or arteriosclerosis.

BROTHERS

de Oliveira, J. M., Mendelsohn, D., Nogueira, C., and Zimmerman, H. A.: Wolff-Parkinson-White Syndrome and Tetralogy of Fallot. Report of a Case. Am. J. Cardiol. **2:** 111 (July), 1958.

A 7 year old boy presented the usual clinical and anatomic features of tetralogy of Fallot with the unique exception that the electrocardiogram repeatedly showed anomalous atrioventricular excitation. Rapid supraventricular tachycardia occurred as a cardiac catheter was placed in the right atrium. Open surgical correction of the defects, aided by total circulatory bypass, was followed by repeated cardiac arrest and death in 18 hours. Autopsy also showed endocardial sclerosis over the ventricular septum, which was considered possibly to be related to the electrocardiographic anomaly.

ROGERS

Bernstein, A., Weiss, F., and Gilbert, L.: Uncomplicated Congenital Mitral Stenosis. Am. J. Cardiol. **2:** 102 (July), 1958.

The forty-eighth instance of congenital mitral stenosis is reported. A 17 months old infant developed heart failure, and the basic disorder was indicated by the roentgenologic finding of a markedly enlarged left atrium. An attempted valvuloplasty by a closed technic was unsuccessful. Autopsy showed a contracted and focally calcified mitral valve that possibly was attributable to an associated fibroelastosis. The findings in this patient are discussed in relation to those of others previously reported.

ROGERS

CORONARY ARTERY DISEASE

Lenegre, J., Himbert, J., and Corcondilas, A.: The Anatomic Lesions of Common Angina Pectoris. Arch. mal. coeur **51:** 481 (May), 1958.

Of 760 consecutive autopsies of cardiac patients, 212 disclosed major coronary sclerosis, and 70 of these patients had shown angina pectoris spontaneously or on exertion. In these 70 hearts, 78 of the major coronary branches (right, left common and anterior, and left circumflex) showed stenosis of 50 per cent to 90 per cent of the lumen, and 116 showed complete or incomplete occlusion; this corresponded to 2.15 occlusions per heart. Myocardial lesions were absent in 15, relatively minor in 29, and major in 26 hearts, which showed a total of 30 myocardial infarctions. Coronary and myocardial lesions had greatest incidence in patients with a very short evolution of angina (several days to 1 month), in those with angina of long duration, not affected by treatment or becoming worse in spite of it, and in those with status anginosus. They were more numerous in spontaneous angina than in angina of effort.

LEPESCHKIN

Rosenberg, B. A., and Malach, M.: Acute Myocardial Infarction in a City Hospital. II. Experience with Anticoagulants. Am. J. Cardiol. **2:** 71 (July), 1958.

The hospital records of all patients having a clear-cut acute myocardial infarction during a 1 year period ending in June 1955 were reviewed. The 66 patients who received anticoagulants (mainly Dicumarol) had the same mortality rate—47 per cent—as the 198 not so treated. The

oups may not have been closely comparable; r example, 88 per cent of the treated patients ere "poor risk" while 74 per cent of the unreated ones were so designated. In the treated oup, 1 instance of major and 4 of minor hemorrage were encountered, suggesting that excessive ticoagulant effect did not often occur. The esent findings are compared with those of prite hospital patients who generally fare considrably better.

ROGERS

chweizer, W.: The Effects of Isopropyl-Isonicotinic Hydrazid (Iproniazid) in Angina Pectoris (Preliminary Report). Cardiologia 33: 40, 1958.

Iproniazid (Marsilid) recommended by Cesarman for the treatment of angina was used in 30 patients. In every patient, the symptoms improved and tolerance to stress increased. In the majority of patients with hypertension, the blood pressure was reduced. However, electrocardiographic alterations attributable to ischemia remained unchanged. Side effects were frequent and consisted in orthostatic hypotension, bradycardia, perspiration, constipation, urinary difficulties, rigidity of spontaneous muscle movement, muscle tremor, and somnolence.

PICK

Legrand, R., Desruelles, J., Merlen, J. F., and Debacker, G.: Long-term Prognosis of Myocardial Infarction. Arch. mal. coeur 51: 362 (April), 1958.

In 100 patients with myocardial infarction followed for 6 months to 5 years, the ballistocardiogram reflected the clinical condition much better than the electrocardiogram. In the 5 patients who died and in 6 who developed heart failure, the ballistocardiogram showed type III and IV. In the 35 patients who developed angina pectoris it usually showed type III, with type II appearing when the complaints subsided. In some patients a more abnormal ballistocardiogram was a sign of approaching death, even when the clinical condition seemed to indicate improvement. More than half the patients were able to return to their work, and in these patients both the ballistocardiogram and the electrocardiogram usually showed marked improvement. An interesting observation concerned the development of pointed upright T waves in 2 cases of anterior and 2 of posterior infarction; this pattern seems to have a good prognosis.

LEPESCHKIN

tmann, D., and Marcus, F. I.: Coronary Insufficiency Associated with Oral Administration of Gall-bladder Dye. New England J. Med. 58: 1244 (June 19), 1958.

Four cases are reported of men with arteriosclerotic heart disease who experienced fatal attacks of coronary insufficiency soon after the ingestion of dye administered orally in preparation for gallbladder x-ray studies. In every case pain of coronary artery origin, either noted for the first time or recurrent, had been present 10 to 30 days before the test was performed, implying a new occlusion or myocardial infarction or both. These cases point out the fact that in patients with recent symptoms of coronary artery disease cholecystography may be a hazardous procedure and should not be performed without positive indications. The possibility of a vasovagal reflex as the mechanism of acute coronary insufficiency in these cases is raised and on this basis it is suggested that when cholecystography must be done in such patients premedication with atropine be employed.

SAGALL

Cossio, P.: The Treatment of Angina Pectoris and Other Muscular Pain due to Ischemia with Iproniazid and Isoniazid. Am. Heart J. 56: 113 (July), 1958.

Iproniazid or Isoniazid was employed in the treatment of 120 patients with angina pectoris and 12 patients with intermittent claudication and impending gangrene of the lower extremities. In one third of the patients with angina pectoris who were treated with iproniazid and in one sixth of the patients treated with isoniazid the attacks of angina subsided entirely or almost entirely after 3 to 7 days. In an additional similar number the frequency, intensity, and duration of attacks diminished although attacks of pain still occurred. These beneficial effects in 95 per cent of the patients lasted for as long as the drug was maintained. In the remaining 5 per cent pain recurred but was of less intensity and duration. The effect on pain due to intermittent claudication was less dramatic. Neither drug was found to have any effect on the natural course of angina pectoris or intermittent claudication. Side effects consisting of faintness, weakness, paresthesias, nervousness, syncope, impotence, or muscular twitchings were reported by two thirds of the patients, occurring in most cases after the third week of treatment. Side effects were more frequent and more intense in the older patients. The author concludes that these drugs are highly effective in the prevention of pain due to ischemia and presents details concerning the dosage, ways of administration, indications, and contraindications.

SAGALL

Verdun de Cantogno, L., and Ramirez de Arellano, J.: Studies on Coronary Circulation. V. Some Aspects of Nervous Influence on Coronary Flow and on Cardiac Metabolism. Arch. Inst. Cardiol. de Mexico **28**: 81 (Feb.), 1958.

The effect of the vagi and of the sympathetic nerves on the coronary sinus flow and on the oxygen uptake of the heart stimulated to increased work was investigated with methods previously reported. Section of the vagi led to disappearance of the increased coronary flow and oxygen consumption obtained in the intact heart. Sympathectomy had no effect on these parameters; the influence of the left vagus was greater than that of the right. It was concluded that a vagal reflex, presumably initiated by baroreceptors located in the cardiac chambers, was stimulated; the efferent pathway would be primarily constituted by coronary vasodilator fibers: it appeared that adrenergic fibers were not an important constituent of the efferent pathway. The modifications of coronary flow secondary to elevation of coronary sinus pressure were also studied. Gradual increase in coronary sinus pressure produced little changes in the intact or sympathectomized animal; when the vagi were severed, a marked decline in blood flow and also in oxygen uptake was noted. Sudden interruption of the venous flow caused a transitory decline in coronary flow, followed by an increase; after vagotomy, a more marked decrease in flow was noted, not followed by a reverse effect. These observations are interpreted as evidence of a vagal reflex initiated by pressure receptors in the coronary sinus and having a vagal vasodilator efferent pathway.

CALABRESI

Reich, N.: The Anatomy of Chest Pain. Am. J. Cardiol. **2**: 95 (July), 1958.

The nerve supply of the major thoracic and upper abdominal structures is reviewed, and the mechanisms and clinical appreciation of pain production therefrom are mentioned. Diagrams of the segmental innervation of the skin and of the cardiac plexus and a sample history form for chest pain evaluation are depicted.

ROGERS

Weissler, A. M., Shapiro, W., and Gaskin, Jr.: Alimentary Lipemia and Coronary Artery Disease in Two Racial Groups. J. Lab. & Clin. Med. **51**: 355 (March), 1958.

Twenty-six white and 26 Negro hospital patients between the ages of 20 and 47 and without evidence of cardiovascular disease were studied on a 3,000 calorie house diet containing 150 Gm. of fat. The studies were performed in the morning following a 10 hour fast. The subjects were given 100 ml. of 10 per cent cream per square meter of body surface area and hourly plasma specimens were taken. No other food was allowed during the 6 hour observation period. The plasma was separated by centrifugation at 2,500 r.p.m. for 15 minutes, and optical densities were determined using a Beckman DU spectrophotometer at a wave length of 650 mμ. Despite the fact that the incidence of proved myocardial infarction in Negroes is 45 per cent of that in Caucasians, in the area from which the studied subjects were taken, there was no difference in the degree of alimentary lipemia or in the number of individual abnormal responses found. The authors conclude that these data are not consistent with the view that intensified alimentary lipemia is a significant predisposing etiologic factor in coronary artery disease.

MAXWELL

Vowles, K. D. J., and Howard, J. M.: Myocardial and Cerebral Infarctions as Postoperative Complications. Brit. M. J. **1**: 1096 (May 10), 1958.

A review of 30 patients who experienced cardiac or cerebral infarction during the 30 days following operation or accidental trauma suggests a biological difference between these 2 processes. Sixty-three per cent of the myocardial infarctions occurred during the operation or within the first 3 postoperative or injury days. All but 23 per cent occurred within a week. On the other hand, the cerebrovascular accidents occurred at random. Preoperatively, two-thirds of the patients in this study had definite clinical evidence of cardiovascular disease. The type of surgery and anesthesia did not seem to bear on the incidence of these complications. However, hypotension did occur in 53 per cent of the patients during surgery and the authors stress this as the most important factor in reduced coronary blood flow. Since atherosclerotic coronary arteries cannot dilate appreciably, the reduction in blood flow associated with the hypotensive state undoubtedly is a major factor in the progression of ischemia. Unlike the heart, during adequate general anesthesia, the oxygen demands of the brain are reduced so that an absolute oxygen deficit rarely occurs. Therefore, a cerebral infarction, when it occurs, is usually not directly related to the surgery or anesthesia. The avoidance of anoxia, hypotension, and increased cardiac work load should prevent many myocardial infarctions. The biological and clinical factors underlying cerebrovascular accidents differ in not being specifically related to the period of trauma. Therefore, attempted prevention requires the empirical application of such measures as adequate oxy-

genation, inhalation of carbon dioxide and the avoidance of undue sedation in arteriosclerotic patients.

KRAUSE

Himbert, J., and Lenegre, J.: Coronary Artery Occlusions and Their Myocardial Consequences in Arteriosclerotic Coronary Heart Disease (Study of 121 Cases). Arch. mal. coeur **51**: 441 (May), 1958.

Of 760 consecutive autopsies in patients with heart disease, a coronary occlusion or a stenosis resulting in at least a 50 per cent reduction of the lumen was found in 211 hearts. In 193 of these a total of 517 occlusions was found: 211 in the left common and anterior descending branches, 167 in the right circumflex branch and 139 in the left. The occlusion was situated in a peripheral section of the artery in 60, in an intermediate section in 165, and in a proximal section in 292, and was caused by thrombosis in 236 and by arteriosclerosis in 281 instances. The average number of infarctions in each heart increased continuously from 0.66 in cases with 1, to 1.40 in those with 6 or more occlusions. Coronary stenosis of less than 50 per cent did not cause any myocardial lesions while 1 exceeding 50 per cent caused them only in part of the cases.

LEPESCHKIN

ELECTROCARDIOGRAPHY, VECTORCARDIOGRAPHY, BALLISTOCARDIOGRAPHY, AND OTHER GRAPHIC TECHNICS

Proctor, M. H., Walker, R. P., Hancock, E. W., and Abelmann, W. H.: The Phonocardiogram in Mitral Valvular Disease. A Correlation of Q-1 and 2 OS Intervals with Findings at Catheterization of the Left Side of the Heart and at Mitral Valvuloplasty. Am. J. Med. **24**:861 (June), 1958.

The reliability and clinical usefulness of 2 phonocardiographic time relationships were tested in 49 patients with mitral valvular disease in whom the Q-1 (beginning of QRS to first heart sound) and 2 OS (second heart sound to opening snap) were compared with data obtained from left heart catheterization and at mitral valvuloplasty. The mean Q-1 interval was prolonged in the entire group with mitral valvular disease compared to that in a group of 23 control patients, but there was considerable overlap. There was little correlation between Q-1 and size of the mitral valve, the end-diastolic pressure gradient across the mitral valve, or the left atrial mean pressure. The interval became shorter in 19 of 21 patients following mitral valvuloplasty. An opening snap was demonstrable in 31 patients. Its absence was associated with extensive calcification of the valve with obliteration of leaflet mobility, predominant regurgitation, or minimal mitral stenosis. A 2 OS of 0.09 second or shorter indicated moderate or severe stenosis, but intervals longer than 0.09 second allowed no conclusion about the degree of stenosis. The 2 OS showed significant positive correlation with left atrial mean pressure and less correlation with the mean diastolic pressure gradient across the mitral valve. The 2OS interval was lengthened in 10 of 20 patients following valvuloplasty. The phonocardiogram was of limited usefulness in the evaluation of mitral valvular disease.

KURLAND

Jouvé, A., Henry, E., Corriol, J., Velasque, P., and Benjamine, R.: The Epicardial Leads in Man with Report of One Case with Anatomic Control. Arch. mal coeur **51**: 626 (July), 1958.

The electrocardiographic findings obtained by multiple epicardial direct unipolar leads in 55 patients are reported; in 1 patient it was possible to verify the electrode placement at autopsy. The electrocardiographic technic used is given. Many leads were obtained from the surface of the left ventricle; only a few from the surface of the right ventricle. On the anterior epicardial surface, in the normal human heart the intrinsic deflection appeared first over the right ventricle, than over paraseptal areas of both chambers, then over the free right ventricular wall, and finally over the left ventricle: the time sequence of activation of the surfaces of the 2 ventricles overlapped, however. A delay over the right ventricle was noted in patients with increased right ventricular load. No correlation was found between the electrocardiographic contour and the thickness of the subjacent myocardium. RS, rS, qRS, or qR patterns were obtained over different points of the left ventricle; there was however an orderly progression of the initial deflection over serial points of the left ventricle.

CALABRESI

Sanna, S., and Mouquin, M.: Investigation on the Electric Configuration of Right Bundle Branch Block (Wilson type) Associated with Marked Right Ventricular Hypertrophy. Arch. mal. coeur **51**: 664 (July), 1958.

The electrocardiograms in 158 patients with right bundle-branch block were compared with the findings of right ventricular hypertrophy at autopsy. The electrocardiograms were classified according to the method of Lepeschkin: 78 belonged to type I, 29 to type II, and 51 to type III: no examples of types IV and V were found.

In 51 of the 78 cases of type I, right ventricular hypertrophy, pure or with dilatation, was found; in 16 the hypertrophy was bilateral, in 6 it was limited to the left ventricle, and in 5 there was no hypertrophy. Of the cases of type II, 7 showed right ventricular hypertrophy; in 7 the hypertrophy was bilateral, in 12 it was limited to the left ventricle; in 3 there was no hypertrophy. Right ventricular hypertrophy was found in 28 cases of type III; in 18 there was bilateral or left ventricular hypertrophy; no hypertrophy was found in 5. It was noted that a marked delay of the intrinsicoid deflection correlated well with right ventricular hypertrophy; this was noted also for a wide area of S_1, resulting from its voltage, but even more from its duration.

CALABRESI

Di Perri, T., and Fabrizi, G.: The Q-I Sound and the II Sound-Opening Snap of Mitral Valve Intervals in Mitral Stenosis before and after Commissurotomy. Cardiologia 33: 97, 1958.

The intervals Q-I sound and the II sound-opening snap were measured in 57 patients with mitral stenosis in direct-writing records of the electrocardiogram and of the logarithmic phonocardiogram. In 9 patients the measurements were repeated after commissurotomy. Fifty normal subjects were studied as controls. In some individuals measurements were obtained also during the Azoulay legs-lifting test. In the normal subjects the Q-I sound interval never exceeded 0.05 second; its duration was a direct function of the cardiac rate. In all patients with mitral stenosis this interval was longer than 0.06 second, and in inverse relation to the cardiac rate; in most patients it became shorter after commissurotomy. The II sound-opening snap interval was directly proportional to the R-R interval; it was prolonged after commissurotomy. The Azoulay test had no demonstrable effect on these measurements.

CALABRESI

van Bogaert, A., Van Genabeek, A., Vandael, J., Arnoldy, M., and Van der Henst, H.: Deviation to the Right of QRS in Clinical Leads Resulting from Left Ventricular Lesion (An Experimental Study). Arch. mal. coeur: 51: 513 (June), 1958.

Right axis deviation is frequently observed in patients with diseases causing increased load limited to the left ventricle. The hypothesis is proposed that this electrocardiographic pattern results from delayed activation of the posterior juxtaseptal left ventricular musculature. To test this hypothesis a localized lesion was produced in dogs by curettage of the endocardial and subendocardial tissue, including the posterior arborizations of the left bundle-branch. The electrocardiographic changes were more evident in hearts in the horizontal position. Because of a late vector involving the posterior wall of the left ventricle and directed anteriorly and inferiorly, deviation of the electric axis to the right was produced. The electrocardiographic changes produced in these experiments were compared with those due to right bundle-branch block and also to posterior displacement of the apex of hearts in the horizontal position. The electrocardiographic changes resulting from similar lesions of the anterior arborizations of the left bundle were also described.

CALABRESI

Merlen, J., Chevat, H., and Germain, G.: Vectorial and Tensorial Interpretation of the Electrocardiogram. Arch. mal coeur 51: 573 (June), 1958.

The fundamentals of the vectorial interpretation of the electrocardiogram and the objections to it are briefly discussed. An interpretation based on non-euclidian geometry is sketched: the electric moment is represented by a tensor rather than by the vector of classic electrocardiography. It is concluded, however, that, although the vectorial interpretation does not fully satisfy the requirement of reproducing each of the scalar electrocardiograms currently obtained and other criteria, the best vectorial systems of leads provide a satisfactory method of analysis of the electrocardiogram.

CALABRESI

Toyoshima, H., Kato, J., Isobe, T., Kutsuna, Y., Nagaya, T., and Saruhashi, Y.: Electrocardiogram and Vectorcardiogram Reconstruction and Its Application to Clinical Diagnosis of Myocardial Infarction Am. Heart J.. 56: 165 (Aug.), 1958.

The characteristics of the electrocardiographic and vectorcardiographic changes in old and fresh myocardial infarctions obtained by a reconstruction method previously described by the author are presented in detail. The changes found by this method closely resembled those reported by previous investigators. In general, RS-T elevations in fresh myocardial infarction corresponded to Q phenomena and reduced R waves in old myocardial infarction, and RS-T depressions in fresh infarction corresponded to augmentation of R waves in old myocardial infarction. The typical changes in the vectorcardiogram comprised displacement of the QRS loops away from the infarcted areas in old infarction and displacement of the RS-T junction directed toward the in-

reted area in fresh infarction. When right ndle-branch block was artificially complicated, waves appeared distinctly in the leads over the farcted area and the initial portion of the QRS op of the vectorcardiogram was displaced away om the infarcted area, but the terminal portion as scarcely displaced at all in most of the left ntricular infarctions and was always inscribed teriorly to the right. When left bundle-branch ock was artificially complicated the characteris- Q waves of myocardial infarction did not ap- ar in the leads over the infarcted area and e QRS loops of the vectorcardiogram showed ly slight displacement away from the infarcted rea in most cases.

SAGALL

Alhomme, P., Welti, J. J., and Facquet, J.: Post-extrasystolic Accentuation of the Murmur of Aortic Stenosis: Its Importance in the Clinical Diagnosis of Systolic Murmurs. Arch. mal. coeur **51**: 493 (May), 1958.

Phonocardiograms of all patients with aortic stenosis observed by the authors showed increased amplitude of the systolic murmur after a long post-extrasystolic pause, or after long pauses in absolute arrhythmia due to atrial fibrillation. This was especially well seen in patients who also had aortic regurgitation, and can be explained by the observation that the aortic pressure was much lower after a long than after a short pause, thus leading to a greater pressure gradient across the aortic valve during the following systole. In the illustrated case the systolic aortic pressure was slightly lower after a long pause. On the contrary, all patients with mitral insufficiency showed little or no change in the intensity of the systolic murmur after long pauses. This can be explained by the observation that the left atrial pressure was approximately the same after a long pause as after a short one . The different behavior after long pauses is an important clue in the differential diagnosis between aortic and mitral systolic murmurs. In 2 patients the systolic murmur was accentuated after a long pause at the base, but not at the apex, and in these patients clinical or anatomic study showed both aortic stenosis and mitral insufficiency.

LEPESCHKIN

rayzel, J.: Electrocardiographic Criteria in the Differential Diagnosis of Pre-excitation (Wolff-Parkinson-White Syndrome) and Arteriosclerotic Heart Disease. New England J. Med. **259**: 369 (Aug. 21), 1958.

A patient with Wolff-Parkinson-White syome is presented emphasizing the fact that omalous atrioventricular excitation may produce Q, S-T, and T changes which simulate those of myocardial infarction. Since the preexcitation phenomenon may also conceal the abnormal Q waves of myocardial necrosis in arteriosclerotic heart disease, normalization of the QRS-complex conduction in this syndrome is essential for the electrocardiographic diagnosis or exclusion of myocardial infarction. Various methods for normalizing excitation are discussed and the effects of atropine, exercise, and quinidine in this regard in this patient are illustrated. The author also points out that after normalization of conduction, the QRS complex remains the most reliable index of infarction and arteriosclerotic heart disease in this patient because the T-wave changes for a number of reasons are not reliable indices of coronary atherosclerosis.

SAGALL

Effert, S.: Differentiation of Positional Anomalies of the Heart by Means of the Electrocardiogram. Ztschr. Kreislaufforsch. **47**: 486 (June), 1958.

A patient with valvular pulmonary stenosis and normal position of the heart developed inversion of the T waves in leads I, II and $V_{3\text{-}5}$ 6 weeks after valvotomy as a result of aseptic pericarditis; the P waves at times became inverted in leads I and $V_{3\text{-}5}$ without appreciable change in the P-R interval, as a result of an atrial ectopic rhythm or an atrial conduction disturbance. A second patient with congenital heart disease but normal heart position showed similar P-wave changes, but the P-R interval was short whenever the P wave was inverted; the T wave remained diphasic or inverted in lead I. If only the tracings with inverted P waves in lead I were available, the pattern would have been indistinguishable from that of mirror-image dextrocardia.

LEPESCHKIN

van Bogaert, A., van Genabeek, A., van der Henst, H., Vandael, J., Arnoldy, M. and Magri, O.: Contribution to the Study of the Mechanism of the Epicardial Q Wave. Arch. mal coeur **51**: 209 (March), 1958.

A unipolar lead from a needle insulated except for its point showed a Q-S deflection with only minimal S-T elevation when the point was in the cavity of the left ventricle and the inner two thirds of the wall; an R wave and marked S-T elevation appeared only in the external one third. A lead from a noninsulated needle showed marked S-T elevation, Q-S deflection only when the needle point was in the cavity, and gradual increase of the R wave as the point was withdrawn toward the epicardial surface. With the point in the cavity, the amplitude of the Q-S deflection was

greatest in the apical region, least in the posterior wall. Areas of complete myocardial necrosis extending from the epicardial surface almost to the endocardial surface were produced by systematic infiltration with 95 per cent carbolic acid. Leads from the center of these areas showed marked elevation of the S-T segment but Q waves appeared in only 12 of 32 experiments; these Q waves did not exceed 3 mm. Ligation of coronary vessels supplying the apex did lead to the appearance of Q waves, especially in leads from the lateral portion of the cyanotic area. Cooling of the apex caused these Q waves, as well as normal Q waves, to become smaller (and also increased S-T elevation), while right bundle-branch block increased them. It is concluded that a necrotic region of ventricular wall cannot be compared to an electric "hole" in this wall, as its conductivity is smaller than that of a noninsulated needle electrode. Leads from the surface of this lesion reflect not only the cavity potential, but also that of normal selections of this wall surrounding them.

LEPESCHKIN

Enescu, I. and Negoita, C.: Considerations on Paroxysmal Ventricular Tachycardia (In Relation to 3 Personal Observations). Arch. mal coeur **51**: 345 (April), 1958.

In 2 patients who had no other cardiac lesions ventricular tachycardia was imitated by atrial flutter with 1:1 conduction and left bundle-branch block. In the first of these, sinus rhythm was restored by quinidine while in the second atrial flutter appeared during the course of treatment of atrial fibrillation with quinidine. When the latter was discontinued, 2:1 atrioventricular block appeared; sinus rhythm was reestablished subsequently by digitalis. The third patient showed "arborization block"; paroxysmal tachycardia in this patient was initiated by single ventricular extrasystoles of the same configuration as that of the wide QRS complexes during tachycardia, and independent P waves could be seen superimposed on the ventricular complexes. This patient died suddenly after leaving the hospital.

LEPESCHKIN

Chevalier, H.: The Electrocardiogram in Metabolic Disturbances. Arch. mal coeur **51**: 233 (March), 1958.

After a review of the literature, 7 personal cases are presented, of which 4 are of interest. A patient with alkalosis showed moderately low T and tall U waves at a serum potassium level of 3.2, but increased slurring of QTS and huge U waves almost completely fused with T waves at a level of 2.2 mEq. per L. Another patient with traumatic anuria showed very low P, pointed T, prolonged P-R, deep S waves in all leads, and a QRS duration of 0.13 second with a serum potassium of 8.5 and a magnesium of 3 mEq. per L. After treatment with the artificial kidney potassium became 5.5 and magnesium 1.6 mEq. per L. and the electrocardiogram became completely normal. A third patient with sarcoidosis and a serum calcium of 6.3 mEq. per L. showed very short T waves with terminal inversion in leads V_1 through V_6, separated by a long isoelectric interval from normally shaped U waves, which appeared at the usual time for the heart rate. In another patient hyperkalemia and hypocalcemia caused the S-T segment to become prolonged but the T wave was short and pointed. It is concluded that the electrocardiogram represents a sensitive index of potassium and calcium imbalance, but it is probably influenced by the concentration gradient across the cell membrane rather than by the absolute concentration; extracellular tissue may influence this gradient by an action similar to that of cation exchange resins. However, because of the multitude of other factors that may affect it, the electrocardiogram must be interpreted with great caution.

LEPESCHKIN

Booth, R. W., Ryan, J. M., and Goodwin, R. M.: A Saline Conductivity Method for Detection of Cardiac Shunts by Indicator-Dilution Technic. Circulation Res. **6**: 142 (March), 1958.

The use of hypertonic saline in the detection of right-to-left shunting is described in 21 patients with congenital heart disease. The advantages over the Evans-blue technic are the unlimited number of determinations that can be made and the lack of interference with oximetric determination. The method suffers the same limitation as any indicator dilution technic in that only the presence but not the location of the shunt can be detected.

AVIADO

Sanghvi, L. M., Misra, S. N., Bannerji, K., and Gupta, K. D.: Electrocardiogram in Chronic Severe Anemia. Am. Heart J. **56**: 79 (July), 1958.

Serial electrocardiograms of 100 patients with anemia of at least 3 months' duration and without other cardiovascular disease were studied. Abnormalities were found in 85 cases. In order of decreasing frequency of incidence these electrocardiographic abnormalities included inversion of T waves, depression of S-T, P changes, prolonged Q-T interval, left ventricular hypertrophy, left ventricular strain, atrial premature beats, ventricular premature beats, prolonged P-R intervals, U-wave changes, atrial tachycardia, and hypopotassemia. Persistence of abnormalities de-

pite cure of the anemia was seen in 36 cases and vas found to have no relation to the age of the patient. In 28 of these, cardiac enlargement persisted. The abnormalities were found more frequently in the female patients. The incidence and nature of the electrocardiographic abnormalities seemed to be closely related to the hemoglobin level and the heart size on admission. The higher incidence of electrocardiographic abnormalities in this series was believed to be due to the greater intensity of the anemia in this group. Several mechanisms of production of the electrocardiographic abnormalities were suggested: temporary coronary insufficiency without actual cardiac damage, subendocardial infarction and reversible cardiac changes, persistent and probably irreversible cardiac changes, congestive heart failure per se, temporary myocardial fatigue due to tachycardia, electrolyte imbalance resulting from diarrhea, and probable abnormal myocardial thiamine metabolism.

SAGALL

Effert, S., Rippert, R., and Schaub, W.: Diagnostic Value of the Electrocardiogram and Phonocardiogram in Ventricular Septal Defects. Ztschr. Kreislaufforsch. **47**: 420 (May), 1958.

Of 11 patients with small defects (less than 1 cm. diameter, shunt less than 3 liters per minute and normal pulmonary arterial pressure) the electrocardiogram was practically normal in 10, but showed deep and slightly wide S waves in leads II and III; one patient showed splintered QRS complexes with deep Q waves in leads I and V_{4-6}. Of 7 patients with medium defects (1 to 1.5 cm., pulmonary pressure exceeding 40 mm.) 2 showed normal findings, 4 showed deep and wide S waves in leads I through III and qR or rSR deflections with tall R waves in V_{1-2} (right activation delay) and 3 showed tall R waves in V_{4-6}. Pointed P waves in leads II and III were found in 2 patients. Of 37 patients with large defects and nearly equal pressures in both ventricles, 10 showed right activation delay and 16 right ventricular hypertrophy pattern, which was accompanied by QS deflection in leads I through III in 3 patients. Incomplete right bundle-branch block was seen in leads V_{5-6} in 1, and a normal finding in 2 patients. P waves were normal in 20, elevated in leads II and III in 10, in I through III in 3, and showed the "mitral" pattern in 3 patients. A systolic murmur of diamond or band shape usually had a maximum at the origin of the fourth left rib and was loudest in small defects, where it could be the only sign. A split first sound was found in one third of the patients.

LEPESCHKIN

Blondeau, M., Himbert, J., and Lenegre, J.: The Electrocardiogram in Angina Pectoris of Effort. Arch mal. coeur **51**: 263 (March), 1958.

Two hundred patients with typical angina appearing only on effort and lasting less than 15 minutes, with a blood pressure less than 160/90 mm. Hg, and free of all other cardiac conditions or drugs that could affect the electrocardiogram, were studied. The pain was retrosternal in 178 and showed radiation (usually brachial, cervical, or dorsal) in 10 patients. Nitroglycerin had a good effect in 52 of 61 patients. A definitely abnormal electrocardiogram was found in 28 per cent; it was most common in patients who had symptoms for less than 1 month or more than 5 years and in those with cardiac enlargement. It included old myocardial infarction patterns (15), bundle-branch block (13), terminal inversion of the T wave (26), and left ventricular hypertrophy (2 cases). Minor abnormalities were found in 41 per cent, especially in women and in persons with a symptom duration of 1 to 5 years; they included low T waves (23) with concave S-T segments (9), peaked, symmetric T waves (17), absent Q waves in leads V_5-V_7 (13), an angle between the QRS complex and T wave exceeding 40° (15), and prolonged Q-T intervals (6 cases). Completely normal electrocardiograms were found in 31 per cent; these were least common when the duration of symptoms was less than 1 year and most common when it was 1 to 6 months and the heart of normal size. Of 38 patients submitted to the exercise test, 25 showed an abnormal electrocardiographic response, 4 a normal response with pain, and 9 a normal response without pain.

LEPESCHKIN

Boyadjian, N., Dechamps, G., and van Dooren, F.: Changes in the Terminal Vector of QRS in Myocardial Infarction. Arch. mal. coeur **51**: 321 (April), 1958.

Electrocardiographic study of 342 patients with infarction showed that in anterior infarction the terminal vector of QRS was deviated to the left in 68 per cent, while in posterior infarction it was normal or deviated to the right in 88 per cent. Of 48 patients where electrocardiograms were available before and after infarction, those with anterior infarction showed left axis deviation of this vector previous to infarction in 66 per cent and after infarction in 84 per cent while those with posterior infarction showed none or right axis deviation previous to infarction in 75 per cent and after infarction in 82 per cent. The changes in the direction of the terminal component are attributed to a conduction disturbance or the boundary of the necrotic area.

LEPESCHKIN

Gillmann, H., and Faust, P.: Sectorcardiography —A New Method of Electrocardiographic Documentation and Comparison. Ztschr. Kreislaufforsch. **47**: 397 (May), 1958.

As vectorcardiography did not prove suitable as a routine method of study, "sectorcardiography" was developed as a rapid and adequately exact method of designation for the spatial cardiac vectors from the standard 12 lead electrocardiogram. In this method, the direction of the highest vectors during P, Q, R, S-T, and T in the frontal plane is subdivided into 12 sectors, according to the direction of these waves in the 6 standard and unipolar limb leads. The direction of these vectors in the horizontal plane is subdivided into 4 sectors, according to the direction of the waves in leads V_1 and V_4. A more exact subdivision in this plane is superfluous because of the errors caused by the eccentric position of the heart. The application of the method is illustrated with several examples.

LEPESCHKIN

So, C. S., Klepzig, H., and Bilger, R.: Studies and Vectorial Considerations on the Value of Supplementary Precordial Leads. Ztschr. Kreislaufforsch. **47**: 429 (May), 1958.

In 40 normal persons and 41 patients without heart disease leads V_{3r} and V_{4r} showed positive waves of QRS that did not exceed 0.5 mv. and were always smaller than the negative waves if these exceeded 0.5 mv. An rSR′ pattern appeared in V_{3r} in 9 per cent and in V_{4r} in 10 per cent. The direction of the T waves in these leads was very variable. In several patients with right ventricular or biventricular hypertrophy R or R′ in these leads (especially in V_{4r}) exceeded the normal limits while other leads showed no signs of right ventricular hypertrophy. The dorsal lead V_8, taken 2 interspaces lower than the conventional level, showed much less variability than the same lead at the conventional level. Persons with normal hearts never showed negative T waves or Q waves deeper than one third of R or wider than 0.04 second in this lead. These patterns may appear in this lead in posterior myocardial infarction even if leads III and aV_F are not definitely abnormal. However, inversion of the T wave in the lower lead V_8 may also appear in left bundle-branch block or in digitalis effect.

LEPESCHKIN

Cisneros, F., Fishleder, B. L., and Sodi Pallares, D.: The Electrocardiogram in Various Rheumatic Defects. Arch. Inst. de Cardiol. de Mexico **28**: 63 (Feb.), 1958.

The electrocardiographic findings in 70 patients with rheumatic valvular defects are reported. Twenty of these patients had pure or predominant mitral stenosis, verified at surgery; 20 had apparently pure mitral regurgitation; 10 had double mitral defects with predominant insufficiency; 20 were patients with pure aortic regurgitation. In pure mitral stenosis the mean axis of the P wave is directed to the left and posteriorly; the P wave in V_1 may be negative; it was of long duration, 0.12 second or more, in 30 per cent of the cases: these changes have never been seen in pure mitral regurgitation. Tall P waves in the standard leads, bifid and diphasic P waves in V_1 were also more common in mitral stenosis than in regurgitation. In mitral stenosis there was right axis deviation of the QRS complex in the frontal plane and deflection to the right and forward in the horizontal plane; therefore the mean solid axis was directed to the right, downward, and anteriorly. The T axis was directed to the left and upward in the frontal plane, to the left and posteriorly in the horizontal plane; hence the solid axis was directed upward, to the left and backward. These findings were of greater significance when the QRS and the T axes were discordant. The transition zone was usually displaced to the left. These changes resulted from hypertrophy and dilatation of the right ventricle, clockwise rotation of the heart, and incomplete right bundle-branch block. In aortic regurgitation the QRS mean axis was oriented to the left, upward, and posteriorly; the T axis was directed downward, anteriorly, and to the left. The transition zone was commonly displaced to the right. This was due to hypertrophy and dilatation of the left ventricle and also to counterclockwise rotation and incomplete left bundle-branch block. In pure or predominant mitral regurgitation the electrocardiographic findings varied between these extremes. The Q wave was frequently absent in the left precordial leads in mitral stenosis; this was interpreted as due to the greater participation of the right ventricle in the anterior surface of the heart and also to the "apex" and the left contour of the heart. The Q wave was instead frequently seen in $V_{2\text{-}4}$ in aortic regurgitation and also in pure mitral regurgitation due to greater participation of the left ventricle in the anterior surface of the heart.

CALABRESI

Dickens, J., and Goldberg, H.: Correlation of the Precordial and Endocardial Ventricular Electrocardiogram. Am. Heart J. **56**: 8 (July), 1958.

Data are presented concerning simultaneously obtained right ventricular endocardial and precordial leads in 50 patients who were studied during cardiac catheterization. This group consisted of 8 normal patients, 6 with pure aortic

stenosis and 36 with congenital heart lesions affecting chiefly the right ventricle. Comparison of these leads indicated that the R′ of both sets of leads may be attributed to upper septal activation. Similar endocardial patterns were obtained in normal subjects and in patients with congenital cardiac lesions, as well as in patients with normal electrocardiographic criteria of right ventricular hypertrophy or of right bundle-branch block thus indicating that the mode of activation of the heart is not altered from the normal in these 2 conditions. In patients showing electrocardiographic evidence of left ventricular hypertrophy an R′ was not recorded in the endocardial leads of the right ventricle. The data indicated that the variation in the precordial patterns found with similar endocardial patterns was a reflection of the influence of cardiac position and the distal effects of left ventricular predominance on the precordial lead. No correlation could be established between the endocardial patterns and the age of the patient, type of cardiac lesion, right ventricular pressure, and type of peripheral electrocardiogram.

SAGALL

Hon, E. H.: The Electronic Evaluation of the Fetal Heart Rate. Am. J. Obst. & Gynec. **75**: 1215 (June), 1958.

The fetal heart rate during labor and delivery was studied by electronic methods employing fetal and maternal electrocardiograms recorded simultaneously by a preamplifier and a cathode ray oscilloscope for careful positioning of the electrodes to obtain a good fetal electrocardiogram. It was found that the fetal heart rate determined throughout contractions provided more accurate information than the average rate determined between contractions. Fetal bradycardia during contractions with the cervix dilated 4 to 8 cm. is normal in vertex presentations. Fetal embarrassment was indicated by bradycardia with contractions at less than 4 cm. or more than 8 cm. dilatation in vertex or breech presentations. Bradycardia persisting between contractions is a late manifestation of fetal distress with serious damage to the fetus. With normal breech and most vertex presentations, fetal heart rate does not slow during contractions. In the minority of vertex presentations, bradycardia may occur with contractions with normal rate restored 10 to 15 seconds later. In these cases, fetal bradycardia is probably related to an increase in intracranial pressure, which in turn is related to the degree of cervical dilatation. It is probable that changes in the instantaneous fetal heart rate represent a sensitive index of fetal distress.

SHUMAN

Jouve, A., Corriol, J., Velasque, P., Benyamine, R., and Peytavy, R.: Comparison of Epicardial and Precordial Leads in Man. Cardiologia 33: 45, 1958.

In 60 patients operated on for mitral commissurotomy, 8 to 126 direct epicardial leads from various ventricular locations were obtained after opening of the pericardium. In each patient, the precordium had been explored before surgery by multiple unipolar leads and charted in an "electric map" of the chest. The precise location of the cardiac chambers in relation to the chest wall was verified in 28 instances with the help of frontal angiocardiograms. Comparison of the 2 lead systems revealed considerable morphologic dissimilarities between direct epicardial leads and the corresponding precordial series. The discrepancy was particularly evident in cases with right ventricular strain. The results of this study failed to confirm Wilson's concept of similarity of epicardial and precordial leads as well as the equivalence of intrinsic and intrinsicoid deflections.

PICK

Torner-Soler, M., Balaguer-Vintro, I., and Morato-Portell, J. M.: The Electrocardiogram in Impending Myocardial Infarction. Cardiologia **32**: 355, 1958.

Electrocardiograms were obtained in 5 patients during prodromal stages of myocardial infarction. In all 5 patients the electrocardiogram was abnormal and showed alterations of the ST-T complexes. According to current concepts, these were interpreted as ischemic alterations involving in 2 patients the subendocardial layers, in 1 the posterior wall and in 2, the anterior wall. In 1 of the latter, the pattern changed to a pattern of anterior wall necrosis after the development of the typical clinical features of myocardial infarction.

PICK

Dupuis, C., Dupuis, B., Adams, F. H., Lind, J., and Peltonen, T.: Further Studies on the Cardiovascular Status of Normal Newborn Infants. IV. Effect of Adrenaline, Acetylcholine, 10 per cent Oxygen, and 100 per cent Oxygen on the Electrocardiogram. J. Pediat. 52: 649 (June), 1958.

A study on 30 infants under 10 days of age is presented. These infants were studied by means of serial electrocardiograms making primary use of unipolar lead B_1. The infants were divided into several groups; all were normal at birth from physical examination. Several groups served as controls, and 1 group of infants was given periodically 10 per cent and 100 per cent

oxygen by mask, and another group was given epinephrine and acetylcholine. The electrocardiographic changes were well recorded. Alteration of the T wave in B_1 took place over a 5 day period and in the older infants administration of epinephrine produced changes in the T wave of B_1 similar to those found in young infants who normally had pulmonary hypertension. No significant change in the tracing was found by the administration of 10 or 100 per cent oxygen. Administration of acetylcholine to younger infants produced no significant changes in the pattern. It is concluded that it is difficult to make any positive statements regarding the nature of pulmonary hypertension in normal newborn infants from the electrocardiographic tracings alone.

HARVEY

Trethewie, E. R.: The E.C.G. of World Class Middle Distance Athletes. Cardiologia **32:** 345, 1958.

During an investigation of the cardiovascular system of Australian athletes, the author noted the frequent occurrence of an electrocardiographic abnormality consisting in splintering and widening of the terminal part of QRS, best seen in lead V_1 or lead B of a special lead system reported previously. Invariably this was observed in middle distance runners and was most marked in 2 outstanding athletes 1 of whom later established the 1 mile world record. This electrocardiographic variety is attributed by the authors to a delay in activation of some parts of the basal portion of the left ventricular myocardium engendered by an altered distribution of the terminal ramifications of the conduction system. such a change in the sequence of ventricular activation can, in the author's opinion, enhance to a significant degree the pumping mechanism of the left ventricle and thus increase cardiac efficiency under stress.

PICK

PHARMACOLOGY

Melville, K. I.: Studies on the Cardiovascular Actions of Chlorpromazine. I. Antiadrenergic and Antifibrillatory Actions. Arch. internat. pharmacodyn. **115:** 278 (June), 1958.

In dogs anesthetized with phenobarbital, chlorpromazine in doses from 1 to 10 mg. per Kg. of body weight induced a transitory fall in blood pressure that was not influenced by vagotomy or by autonomic drugs: it was suggested that this effect resulted from direct action of the drug upon the heart or blood vessels; tachycardia and elevation of the T wave in the electrocardiogram, however, were abolished by vagotomy or atropinization. A single large dose of chlorpromazine (10 mg. per Kg.) caused a marked fall in blood pressure with transient bradycardia and inversion of the T wave: vagotomy or atropinization did not prevent these changes. No toxic cumulative action was noted: following prolonged administration of the drug, the animals died in a shocklike state due to the persistent hypotension. Chlorpromazine in small doses antagonized the pressor effect of norepinephrine; the pressor effect of epinephrine was inverted. This inversion was not obtained however in cats similarly treated in which the brain had been destroyed; because of this, a central nervous system effect or a reflex mechanism was suggested. Chlorpromazine in small doses also prevented the cardiac arrhythmias and fibrillation following injections of epinephrine during chloroform inhalation; even in much higher doses the drug did not prevent the arrhythmias produced by pressor pituitary extract or by ouabain. It was suggested that the antagonism to chloroform-epinephrine arrhythmias was not a direct effect of chlorpromazine on the heart, but possibly involved a reflex or central nervous system action.

CALABRESI

Levy, B., and Koelle, G. B.: The Cardiovascular and Respiratory Actions of Rauwolscine. J. Pharmacol. & Exper. Therap. **123:** 278 (Aug.), 1958.

The mechanism involved in the cardiovascular effects of rauwolscine were studied in dogs and cats. It was found to be a short-acting, reversible type of adrenergic blocking agent. It produced reversal of the pressor response to epinephrine and reduction of the pressor response to levarterenol in both the dog and cat. Doses of rauwolscine that produced epinephrine reversal of the blood pressure did not reduce the pressor response to bilateral carotid occlusion. Much larger doses of rauwolscine were needed to inhibit contraction of the nictitating membrane than to produce epinephrine reversal. The drug exerted a peripheral vasodilator effect on both the innervated and denervated hind limb of the dog. It produced tachypnea consistently in the dog but not in the cat. The effects of rauwolscine on the heart rate were not marked. The cat showed no significant change in rate even during hypotension. The dog showed a transient bradycardia on occasion.

RINZLER

Melville, K. I., and Drapeau, J. V.: Studies on the Cardiovascular Actions of Chlorpromazine. II. Effects on Cardiac Output, Coronary Flow and Heart Contractions. Arch. internat. pharmacodyn. **115:** 306 (June), 1958.

In 13 dog heart-lung preparations it was observed that small doses of chlorpomazine had no effect, higher doses produced transient depression of the cardiac output and still larger doses induced cardiac arrest. These effects were not irreversible and could be antagonized by epinephrine. Small doses of chlorpromazine did not inhibit the cardiac effects of acetylcholine, and even high doses only diminished these effects. In the isolated and perfused rabbit heart chlorpromazine induced depression of heart contractions and coronary dilatation; the stimulating action of epinephrine or norepinephrine was not completely blocked even by large doses. In the isolated perfused frog heart the negative inotropic effect of chlorpromazine was also observed; this effect could not be prevented by epinephrine or norepinephrine; it could be transitorily overcome by the simultaneous perfusion of ouabain, but the ultimate toxic effect of ouabin was not prevented. It was concluded that chlorpromazine exerted no specific anti-adrenergic action on the dog, rabbit, or frog heart, but had a depressant effect on the myocardium and conduction system, and also on the musculature of the coronary vessels.

CALABRESI

Litchfield, J. W., Manley, K. A., and Polak, A.: Stokes-Adams Attacks Treated with Corticotrophin. Lancet **1**: 935 (May 3), 1958.

Three patients with Stokes-Adams attacks who failed to respond to customary measures were treated with intramuscular corticotrophin. All improved strikingly within a few hours. The mechanisms of improvement are unknown although in these 3 patients, age 35 to 45, the possibility of an underlying inflammation of the bundle of His was postulated.

KURLAND

Maren, T. H.: Carbonic Anhydrase Inhibition. IX. Augmentation of the Renal Effect of Meralluride by Acetazolamide. J. Pharmacol. & Exper. Therap. **123**: 311 (Aug.), 1958.

The augmentation of the renal effect of meralluride by acetazolamide was studied in beagles. Acetazolamide, given at 0 time and at 12 hours, augmented the effect of meralluride when given at 24 hours and promoted the renal excretion of sodium, chloride, and water. This augmentation appeared to be due to prior excretion of carbonic acid following acetazolamide, which resulted in a metabolic acidosis that could be reflected in acidosis of the renal cells. This could occur in the presence of normal plasma chloride concentration. When the 2 drugs are given simultaneously, chloride excretion may be less than that following meralluride alone. For maximal chloruretic effects, it is advised that the 2 agents not be given together. The most effective regimen for a 48 hour net sodium and chloride removal is administration of acetazolamide on the first day and of meralluride on the second day.

RINZLER

Weaver, L. C., Alexander, W. M., Abreu, B. E., Richards, A. B., Jones, W. R., and Begley, R. W.: The Mechanism of the Hypotensive Action of Narcotine Hydrochloride. J. Pharmacol. & Exper. Therap. **123**: 287 (Aug.), 1958.

This report deals with a systematic study of the cardiovascular effects of narcotine hydrochloride with some comparison to those of related compounds. It produces systemic vasodepression in dogs which is incompletely blocked by diphenhydramine and is not affected by atropinization, midcervical vagotomy or carotid sinus and body denervation. Narcotine in the intact dog proved a relatively potent vasodilator with a moderately long duration of action. It increased coronary and femoral blood flow. Tachyphylaxis to the vasodepressive effect of narcotine could be produced following intravenous administration. Tachyphlaxis to the systemic hypotensive action of papaverine hydrochloride, ethaverine hydrochloride, or dioxylinephosphate did not occur. Narcontine produced bronchoconstriction. These effects of narcotine were attributed to liberation of histamine.

RINZLER

Maxwell, R. A., Plummer, A. J., Ross, S. D., Daniel, A. I., and Seneider, F.: Factors Affecting the Blood Pressure Response of Mammals to the Ganglionic Blocking Agent, Chlorisondamine Chloride. J. Pharmacol. & Exper. Therap. **123**: 238 (July), 1958.

Chlorisondamine chloride was used as a model for ganglionic-blocking agents to observe its effects on the response to the drug of different species of test animals, the presence and absence of barbiturate anesthesia, and the type of experimental hypertension. It was found that the blood pressure of the unanesthetized normotensive monkey and rabbit showed a definite and sustained fall in systolic and diastolic levels after intravenous administration of the drug. On the other hand, the blood pressure of the dog and rat under the same conditions did not respond with a persistent fall. In contrast, normotensive dogs, after pentobarbital, showed a fall in systolic and diastolic pressures associated with a relative bradycardia following the ganglionic-blocking agent administration; rats, after Dial-Urethane, likewise showed a fall in blood pressure following

injection of chlorisondamine chloride. The dog, in the malignant phase of renal hypertension, responded with a sustained systolic and diastolic decline following injection of the ganglionic-blocking agent. Studies of the cardiac output, mean blood pressure, peripheral resistance, and cardiac volume indicated that the barbiturates interfere with compensatory mechanisms that normally function in the normotensive dog and rat during ganglionic blockade and that these compensatory mechanisms appeared to be less predominant in the monkey and rabbit.

RINZLER

Burn, J. H., and Rand, M. J.: Noradrenaline in Artery Walls and its Dispersal by Reserpine. Brit. M. J. 1: 903 (April 19), 1958.

The origin of norepinephrine which was found in the walls of arteries is not definitely known. It has been suggested that it comes out steadily from the sympathetic nerve fibers. The authors offer evidence that the accumulation of norepinephrine can be dispersed by the action of reserpine in the course of several hours. When this occurs, nicotine and acetylcholine, which are usually vasoconstrictive, lose this action on the blood vessel involved. It might be that this action of nicotine, namely the release of norepinephrine from the vessel, accounts for the pain that occurs when a patient with thromboangiitis obliterans smokes. On the basis of their experiments, the authors suggest that reserpine might be of value in peripheral vasoconstrictive disease states. In this respect, the use of reserpine is limited by its effect on the central nervous system.

KRAUSE

Grettve, J., and Johansson, B.: Digitalis Allergy: Review of the Literature and Report of a Case. Cardiologia 32: 374, 1958.

A 60 year old woman who had taken tablets of digitalis leaf for many years developed itching and a skin rash consisting in an exanthema, at first papular, later bullous in appearance, associated with eosinophilia. Idiosyncrasy could be demonstrated to injection of a number of commercial digitalis preparations, including acetyl digitoxin, cedilanid, and digoxin, but skin tests were negative. Antihistaminic durgs failed to control the allergic reaction.

PICK

PHYSIOLOGY

Selzer, A., and Sudrann, R. B.: Reliability of the Determination of Cardiac Output in Man by Means of the Fick Principle. Circulation Res. 6: 485 (July), 1958.

There was a satisfactory reproducibility of the measurements of cardiac output in 167 unselected cases. The median error of 2 separate determinations using the Fick principle within a 15 minute time period was 8.6 per cent. The potential error due to phasic variations of blood oxygen content was of no major importance in the determination of cardiac output. In spite of the complexity of the procedures of cardiac catheterization, a satisfactory steady state occurred in the majority of patients.

AVIADO

von Euler, U. S., and Lishajko, F.: Catechol amines in the Vascular Wall. Acta physiol. scandinav. 42: 333, 1958.

This report deals with the presence of norepinephrine and its congeners chiefly in splenic and lung vessels. Bovine splenic arteries and veins contain about 0.3 to 0.4 μg. of norepinephrine per gram. Bovine pulmonary vessels with a diameter of 2 mm. and above contain amounts of catechol amines similar to those of splenic vessels. Lung vessels and other vessels from the dog, however, contain larger amounts of catechol amines than those from bovine sources. There is a differential distribution of amines even within the lung, for large bovine lung vessels contain 10 times more norepinephrine than peripheral lung tissue. Chromotographic separation of catechol substances in splenic and pulmonary vessels indicate the presence of dihydroxyphenyl acetic acid, dihydroxymandelic acid, dopamine and norepinephrine which are similar for the 2 kinds of vessels but differ greatly from the relative and absolute amounts found in lung tissue.

RINZLER

Harris, E. A., and Thomson, J. G.: The Pulmonary Ventilation and Heart Rate during Exercise in Healthy Old Age. Clin. Sc. 17: 349, 1958.

Pulmonary ventilation, tidal volume, alveolar carbon dioxide tension, respiratory exchange, and heart rate in response to exercise of different intensities have been measured in 5 men, age 70 to 70 years, and compared to a group of students age 19 to 26. The older group showed a higher total ventilation for any given load attained by a higher respiratory frequency with a somewhat lower mean tidal volume and a little larger physiologic dead space. Alveolar carbon dioxide pressure was the same in the 2 groups. The difference in dead space diminished with increasing rate of work. The old men also showed a higher exercise heart rate at an oxygen uptake around 1500 ml. per minute due to a slow rise in rate between the end of the first half minute and the end of the fourth minute.

KURLAND

oltke, E., and Worning, H.: Studies on the Hydrogen Ion Concentration, Oxygen Saturation, and Carbon Dioxide Tension of the Arterial Blood in Patients with Cardiac Dyspnea. Acta med. scandinav. 5: 397, 1958.

The hydrogen ion concentration, oxygen saturation, and carbon dioxide tension of the arterial blood were investigated in 55 patients with cardiac dyspnea and, for comparison, in 55 patients with dyspnea due to chronic pulmonary disease. The majority of patients with pulmonary dyspnea showed reduced oxygen saturation, increased carbon dioxide tension, and a decrease in pH. Patients with cardiac dyspnea exhibited normal or slightly reduced oxygen saturation, normal or reduced carbon dioxide tension and a pH either normal or shifted toward the alkaline side. In cardiac dyspnea there was no significant difference in oxygen saturation and carbon dioxide tension between patients with mild or severe dyspnea at rest except in those with an arterial oxygen saturation greater than 93 per cent. In this latter group carbon dioxide tension was significantly lower in those with severe rather than mild dyspnea at rest. In patients with pulmonary dyspnea the oxygen saturation was significantly lower and the carbon dioxide tension significantly higher in the presence of severe dyspnea as opposed to mild dyspnea at rest. The dyspnea that occurs in congestive heart failure cannot be said to be due exclusively to changes in the blood chemical studies that were done. The authors conclude that cardiac dyspnea is probably due to alterations in the pulmonary arterial pressure.

BROTHERS

Scherf, D., Blumenfeld, S., Yildiz, M., and Jody, A.: The Effect on Atrial Impulse Formation of a Hypertonic Solution of Sodium Chloride Applied Focally. Am. Heart J. 56: 236 (August), 1958.

It was found in mongrel dogs that it was possible to induce brief runs of atrial flutter or atrial fibrillation with great regularity by cardiac stimulation of the vagus nerve after about 0.05 ml. of a solution of 20 per cent sodium chloride in water had been injected subepicardially over the area of the sinus node (taenia terminalis). In most instances, the flutter or fibrillation started between the QRS complex and the T wave of an escaped beat during the vagus stimulation. These findings indicate that the abundance of sodium in these experiments enhanced and created the formation of ectopic atrial impulse and that if ectopic atrial beats occurred during the vagus stimulation, any beat appearing during the vulnerable phase of a preceding one may lead to the repetitive firing and cause atrial fibrillation or flutter. The application of a broad ligature across the sinus node area and the encompassing tissue to the right and left of the taenia terminalia did not interrupt or alter existing atrial flutter or fibrillation. This observation was interpreted as precluding the possibility that these attacks were due to a circus wave traveling up or down the sinus node or around the intercaval bridge.

SAGALL

Grosse-Brockhoff, F. and Wolter, H. H.: The Filling Pressure at the End of Diastole in Chronic Pressure and Volume Overload of the Right Ventricle. Ztschr. Kreislaufforsch. 47: 481 (June), 1958.

In 71 patients with pure pulmonary stenosis, right atrial and ventricular pressure at the beginning of the QRS complex of the electrocardiogram was found to increase with the maximal right ventricular systolic pressure. A similar behavior was found for the amplitude of the atrial contraction wave in the right atrial pressure curve. The mean diastolic pressure showed no elevation unless there were signs of right ventricular failure. On the contrary, in 28 patients with atrial septal defects there was no definite relation between the increase in right ventricular output and the right atrial pressure at the end of diastole or the amplitude of the atrial contraction wave.

LEPESCHKIN

Edwards, A. W. T., and Korner, P. I.: Factors Determining the Dispersion of Dye in Indicator Dilution Curves in the Normal Mammalian Circulation. Clin. Sc. 17: 265, 1958.

Dye-dilution curves were obtained in 4 dogs following injection at different sites and levels of flow and volume in order to show that, in normal animals, the anatomy of the circulation between injection and sampling sites was a determinant of the contour of the dye curve. Volume between injection and sampling sites was varied by altering the injection site, which increased the volume and the anatomic path length, and by bleeding, which altered the volume without changing the path length. When dye was injected into the pulmonary artery, the curves had a larger variance, an earlier appearance time, and a lower peak concentration for a given flow and volume than was observed following injection into the inferior vena cava. Reduction in mean flow and volume by bleeding did not alter the equations relating variance of the curves to flow and volume.

KURLAND

Fowler, N. O., Bloom, W. L., and Ward, J. A.: Hemodynamic Effects of Hypervolemia with and without Anemia. Circulation Res. **6:** 163 (March), 1958.

Experiments in dogs suggest that the increase in cardiac output following infusion of dextran solution is related to the anemia produced thereby and not to the expansion of whole blood volume or to the increase in cardiac filling pressure. This hypothesis is based on the observation that hypervolemia without anemia does not cause an increase in output, whereas hypervolemia with anemia increases output. The ultimate mechanism for the increase in output has not yet been identified but the most attractive one is the release of a cardiac stimulant humoral agent by anemia.

AVIADO

Cannata, D., and Narbone, N. B.: Clinical Observation on the Role of the Vegetative Nervous System in the Pathogenesis of Atrial Fibrillation. Cardiologia **32:** 329, 1958.

The authors reviewed the literature dealing with experimental and clinical observations on the relationship of neurovegatative stimuli and atrial flutter and fibrillation. Usually vagal stimulation predisposes to, or triggers the onset of these disorders of rhythm, but on rare occasions, with special conditions of reactivity of the myocardium, increased vagal tone may terminate the atrial arrhythmia. Two clinical examples are presented in which paroxsyms of atrial fibrillation could be induced by parasympathetic stimulation. This was demonstrated in records revealing consistently slowing of the sinus rate prior to the onset of fibrillation, multiplication of atrial premature systoles and short bursts of atrial fibrillation under carotid sinus pressure, abolition of fibrillation subsequent to atropine injection and appearance and disappearance of fibrillation independent of changes in posture.

PICK

Beznak, M.: Cardiac Output in Rats During the Development of Cardiac Hypertrophy. Circulation Res. **6:** 207 (March), 1958.

Aortic constriction in rats caused an immediate decrease in cardiac output. After 1 week, the hypertrophied heart maintained a nearly normal hemodynamic situation. The hypertrophied heart was not only enlarged but was characterized by an increase in "reserve force," i.e., the maximum output induced by infusion. The actual stimulus for the hypertrophy was not revealed by the experiments.

AVIADO

Cunesco, V.: Hemodynamic Aspects of Cardiac Arrhythmias. Arch. mal. coeur **51:** 329 (April) 1958.

Extrasystoles appearing during the ejectio phase of the preceding systole, as evidenced in th pulmonary artery pressure pulse, caused a rise i pressure superimposed on this systole and re sulted in an increase in its amplitude and dura tion. Extrasystoles appearing during the pha of relaxation produced a rise in pressure of greatly reduced amplitude and duration; showe an increased period of mechanical latency usuall not accompanied by ejection into the great ve sels. Extrasystoles appearing during the fillin period were characterized by prolongation of th latent period and shortening of ejection. Th postextrasystolic beat showed decreased latenc period and increased duration and amplitude o contraction; these changes may be present als in the subsequent beat. No difference was foun between atrial and ventricular extrasystoles. I atrial fibrillation the ventricular diastolic base line was smooth, while in atrial flutter it showed deviations coinciding with the flutter waves.

LEPESCHKIN

Liebau, G.: Cause and Effect of the High Pressure Gradient in the Arterioles. Ztschr. Kreislaufforsch. **47:** 385 (May), 1958.

It is calculated that the total resistance to flow is greater in the capillaries than in the arterioles, but this would not explain the fact that the decrease in mean arterial pressure is greater in arterioles than in the capillaries. Observation of blood flow in the ocular fundus shows that pulsation of the arterioles is largely transmitted to the venules that accompany them. This transmission could have great importance in facilitating blood flow in these veins, and would also account for the considerable pressure gradient in the arterioles. The transmission of arterial pulse to the veins would also result in an immediate increase of venous return whenever there is a sudden rise in heart output.

LEPESCHKIN

Walton, R. P., and Darby, T. D.: Circulatory Effects of Salicylates. Circulation Res. **6:** 155 (March), 1958.

The injection of sodium salicylate (100 mg. pe Kg.) consistently produced a prompt increase i heart contractile force in anesthetized dogs. Th effect, however, was moderate if compared wit typical stimulant drugs such as digitalis, xan thines, and sympathomimetic amines. There is little reason to consider that this limited increas in heart force has any significant clinical impo tance beyond the fact that this may be taken a

a indication that the usual doses of salicylates robably do not seriously depress myocardial contractility.

AVIADO

RENAL AND ELECTROLYTE EFFECTS ON THE CIRCULATION

Fordyke, R. A., and Pearce, M. L.: Renal Adaptations to Postural Changes in Chronic Congestive Heart Failure. Am. Heart J. **56**: 202 (August), 1958.

The renal response to postural changes on the tilt table was studied in 17 patients in chronic congestive heart failure. In normal individuals the acute adjustment to the standing position included a decrease in the renal plasma flow in the glomerular filtration rate and in the urinary rate of excretion of sodium and water. Patients with a mild degree of congestive failure showed a response similar to that of normal individuals. As congestive failure became more marked this orthostatic response was reduced and in certain patients with severe heart failure there was essentially no response to the tilt position.

SAGALL

Hutt, M. S. R., Pinninger, J. L., and de Wardener, H. E.: The Relationship between the Clinical and the Histological Features of Acute Glomerular Nephritis. Quart. J. Med. **27**: 265 (April), 1958.

Renal biopsies were performed 5 to 17 days after the onset of illness in 15 patients with acute glomerulonephritis, and the clinical features were compared with the structural changes. In general, there was a broad measure of agreement regarding severity between the clinical and histologic features. Proteinuria and hematuria indicated structural lesions of the glomerular tufts, and hypertension was in general also related to glomerular disease. Changes in the tufts are accompanied by decreased creatinine clearance, which appeared to be a more reliable indication of structural abnormality than the blood urea. Impairment of the ability to concentrate was an indication of microscopically evident damage in the distal tubules. A sedimentation rate greater than 55 mm. in 1 hour was good evidence of widespread renal damage with interstitial and tubular lesions. Only 2 patients had proteinuria for more than a year; both had numerous tubular lesions.

KURLAND

Holland, W. C., and Klein, R. L.: Effects of Temperature Na and K Concentration and Quinidine on Transmembrane Flux of K^{42} and Incidence of Atrial Fibrillation. Circulation Res. **6**: 516 (July), 1958.

Quantitative studies of the isolated rabbit atrium have revealed that the onset of fibrillation is accompanied by a net loss of potassium. Fibrillation and its associated flux changes were inhibited by a decrease in temperature, a decrease in extracellular sodium concentration, an increase in intracellular potassium concentration, and the presence of quinidine. The data presented did not establish whether the permeability change was the cause or the result of the initiation of arrhythmia.

AVIADO

Keyl, A. C.: Digitalis Antagonism. Arch. Int. Med. **101**: 849 (May), 1958.

Based on data obtained from dogs poisoned by strophanthin, an attempt was made to differentiate between mild and severe digitalis intoxication. This was studied by means of the response to the antagonism of the potassium ion. It has been postulated that in digitalis intoxication, the primary defect may involve interference with active transport of potassium to the myocardial cells and this interference is in proportion to the dose of digitalis. When digitalis intoxication is mild, it seems that the use of potassium in any form will correct the ionic deficit. However, when digitalis intoxication is severe, the anion of the potassium salt may be a factor in determining its effectiveness. In particular, the authors were impressed with the results obtained when potassium was used as the glutamate. They speculate on the mechanism of potassium gluterate and glutamate reversal of strophanthin toxicity under circumstances where the chloride was ineffective. It is suggested that the glutamate ion may operate by its ability to promote active transport of potassium to the depleted cells.

KRAUSE

Riddle, M., Gardner, F., Beswick, I., and Filshie, I.: Nephrotic Syndrome Complicating Mercurial Diuretic Therapy. Brit. M. J. **1**: 1274 (May 31), 1958.

Mercurial diuretics are an important and valuable adjunct in the treatment of congestive heart failure. However, they are potentially dangerous because of their action on the renal tubular epithelium. There have been scattered reports on the occurrence of the nephrotic syndrome after prolonged administration of mercurial diuretics. The authors present 5 cases of the nephrotic syndrome, 3 of them fatal, which appeared following the use of mercurial diuretics. The fatal cases were autopsied and each presented similar pathologic changes in the kidneys, resembling in quality those seen in acute poisoning with mercuric chloride. Furthermore, none of these cases had

evidence of kidney disease before the administration of the mercurial and each had a normal urine before treatment was begun. Additional convincing evidence was the fact that at autopsy, an excess of mercury was found in the renal tubules in 2 cases and, furthermore, no cause other than mercurial damage to the kidneys was found. Early recognition of this condition is of the utmost importance if a fatal outcome is to be avoided. Close supervision of patients treated with mercurial diuretics, including regular urine analysis is essential. The most useful evidence of tubular damage is the persistence of albumin despite a satisfactory diuresis in response to mercurial therapy.

KRAUSE

Melville, K. I., and Korol, B.: Cardiac Drug Responses and Potassium Shifts. Studies on the Interrelated Effects of Drugs on Coronary Flow, Heart Action and Cardiac Potassium Movement (Section I). Am. J. Cardiol. **2**: 81 (July), 1958.

Isolated rabbit heart preparations were studied. The administration of epinephrine, norepinephrine, isoproterenol, or theophylline during perfusion via the aorta with normal Locke's solution generally increased the strength and rate of contraction, dilated the coronary arteries, and led to a net loss of potassium from the heart. Reduction in the potassium content of the Locke's solution by 75 per cent resulted in a greater degree of cardiac stimulation and coronary dilatation when the above drugs were given; at the same time the mean potassium shifts from the hearts were not significantly changed. Perfusion with potassium-free Locke's solution regularly was followed by a rapidly progressive increase in rate and amplitude of contraction and increased coronary flow ending in ventricular fibrillation in 10 to 15 minutes. A number of related experiments are reviewed.

ROGERS

Flowers, C. E.: A Carbonic Anhydrase Inhibitor as a Diuretic in Obstetrics. Am. J. Obst. & Gynec. **75**: 1180 (June), 1958.

The effect of Diamox upon urine volume, body weight, and sodium and potassium excretions was evaluated using the diuretic index of Kattus. The drug was found to have virtually no effect upon normal pregnant patients with no edema or hypertension. In those with edema but without hypertension, Diamox produced a more rapid loss of fluid and electrolyte than did treatment with low-sodium diets (700 to 1000 mg.). However, unless sodium intake was restricted, the use of Diamox was associated with subsequent retention of sodium and water. In 20 patients with edema and hypertension a favorable response occurred with the use of Diamox; however, the enhanced excretion of sodium appeared to be unimportant in the management of these patients. There was no clinical improvement until after delivery. The patients receiving Diamox had no greater hypotensive response than those treated without specific therapy. The drug was ineffectual in patients with severe toxemia of pregnancy, eclampsia, reduced glomerular filtration, impaired renal function, or a profound electrolyte disturbance.

SHERMAN

RHEUMATIC FEVER

Breese, B. B., and Disney, F. A.: Penicillin in the Treatment of Streptococcal Infections: A Comparison of Effectiveness of Five Different Oral and One Parenteral Form. New England J. Med. **259**: 57 (July 10), 1958.

A comparison was made of the effectiveness in the treatment of 611 children of beta-hemolytic streptococcal infections of 1 form of parenteral penicillin (a single intramuscular injection of 600,000 units of benzathine penicillin G) and 5 different oral preparations (benzathine penicillin G tablets, penicillin G with probenecid suspension, penicillin G with probenecid tablets, buffered potassium penicillin G tablets, and penicillin V). Treatment with the oral preparations was maintained for 10 days. Penicillin in any of the forms used was found to be an effective agent in the immediate treatment of streptococcal infections. Study of the "cure rate" at the end of 2 months and the relapse rate within 25 days indicated that the single intramuscular injection of 600,000 units of benzathine penicillin G was superior to the oral forms of penicillin, therapeutically, prophylactically, in cost and in avoidance of the problem of oral administration of drugs to children. The chief disadvantage comprised the painful local reaction frequently observed and the psychologic trauma of an injection. Among the oral preparations no single preparation was found to be significantly superior to the others. There was no significant difference between the oral and intramuscular forms of penicillin in the allergic reaction rate. The authors conclude that the first choice of treatment of streptococcal infections in children is a single intramuscular dose of 600,000 units of benzathine penicillin G, but if an oral preparation is to be used cost factors would make buffered penicillin G in a dosage of 800,000 units daily for 10 days the first choice.

SAGALL

Schreier, A. J., Hockett, V. E., and Seal, J. R.: Mass Prophylaxis of Epidemic Streptococcal Infections with Benzathine Penicillin G: I. Experience at a Naval Training during the Winter of 1955-1956. New England J. Med. **258**: 1231 (June 19), 1958.

The results of the use of a single 600,000-unit injection of benzathine penicillin to navy recruits in an attempt to minimize streptococcal infection and rheumatic fever are reported. The injection was administered to 19,561 recruits arriving at one training station between November 22, 1955, and April 14, 1956. This program appeared to have reduced the incidence of streptococcal infections over that experienced in previous winters when prophylaxis either was not used or employed only after an outbreak had occurred. The incidence of rheumatic fever was also lower in those recruits who received prophylaxis. The single 600,000-unit injection of benzathine penicillin apparently afforded a high degree of individual protection against streptococcal infection for a period of about 3½ weeks. There were 145 clinical episodes adjudged to be sensitivity reactions after prophylactic benzathine penicillin. This rate of 0.74 per cent was very close to that found in a smaller previous experiment at this station and was about twice that observed after mass oral penicillin. No serious reactions were observed and the majority of sensitivity reactions were mild and transient with a good response to antihistaminic drugs.

SAGALL

McFarland, R. B., Colvin, V. G., and Seal J. R.: Mass Prophylaxis of Epidemic Streptococcal Infections with Benzathine Penicillin G: II. Experience at a Naval Training Center during the Winter of 1956-57. New England J. Med. **258**: 1277 (June 26), 1958.

The experience with a mass prophylactic program employing a single injection of benzathine penicillin to recruits at a naval training station during the fourth week of their 70 day stay is reported. Annual epidemics of streptococcal infections and rheumatic fever had previously been a problem at this station. The probable effectiveness of the prophylactic program with benzathine penicillin during the winter of 1956 and 1957 was indicated by the lowest incidence of streptococcal disease in the history of the station and by the fact that only 3 cases of rheumatic fever occurred among the 20,000 men at risk. Dosages of both 600,000 and 1,200,000 units of benzathine penicillin were used, but the larger dose did not appear to increase the degree or duration of protection. Adverse sensitivity reactions to penicillin were not a deterrent to the program.

SAGALL

McFarland, R. B.: Reactions to Benzathine Penicillin. New England J. Med. **259**: 62 (July 10), 1958.

Allergic penicillin reactions observed in 175 patients resulting from a total of 12,858 single injections of benzathine penicillin G given to military personnel for prophylaxis of streptococcal infections are described. This was a reaction rate of 1.3 per cent. The reactions observed ranged all the way from mild urticaria, lasting 1 or 2 days, to the full picture of serum sickness, lasting several weeks. Dermatologic manifestations only occurred in 21 per cent of this group while more severe reactions developed in 130 patients or 76 per cent. Fourteen patients (1 out of a 1,000 men injected) had reactions severe enough to require cortisone therapy. The reactions were of the delayed type and usually became manifest 8 to 15 days after the injection, although some occurred as early as the day of injection and some as late as 48 days after injection. The signs and symptoms of the allergic reactions tended to be prolonged and commonly recurred after they had temporarily abated, particularly in areas subject to trauma. Response to steroid therapy was prompt, but antihistamine therapy appeared to have only a slight effect in diminishing the length of illness caused by the allergy. Many reactions were observed to clear rapidly without therapy.

SAGALL

Catanzaro, F. J., Rammelkamp, C. H., Jr., and Chamovitz, R.: Prevention of Rheumatic Fever by Treatment of Streptococcal Infections. II. Factors Responsible for Failures. New England J. Med. **259**: 51 (July 10), 1958.

At a military hospital 5198 patients who received treatment with an antibiotic or sulfadiazine for streptococcal tonsillitis or pharyngitis were studied to determine the factors responsible for the development of rheumatic fever. Of this group 76 later developed acute rheumatic fever despite therapy. Eighteen of these patients were excluded from the study because the historical and bacteriologic evidence did not clearly indicate that the observed and treated streptococcal infection was the primary precipitating factor for their rheumatic fever. In 9 patients acute rheumatic fever developed during the first 72 hours of the acute streptococcal illness and treatment would not be expected to prevent rheumatic fever, since it was already present. Study of the various factors concerned in the remaining 49 patients with acute rheumatic fever showed that the primary cause of failure to prevent rheumatic fever was the fact that the infecting type of streptococcus was not eliminated by therapy. Other factors of lesser importance were the acqui-

sition of a new infection after therapy and a history of previous attacks of rheumatic fever or of recent streptococcal infections.

SAGALL

Costero, I., Barroso-Moguel, R., Chevez, A., Monroy, G., and Contreras, R.: The Lesions of Rheumatic Fever in Patients Treated with Cortisone. I. Endomyocarditis. Arch. Ints. Cardiol. México **28**: 155 (March-April), 1958.

A report is presented of the pathologic changes found in the hearts of 30 patients with severe rheumatic fever who had been treated with cortisone or its analogues and died because of rheumatic carditis. Studies of other organs and also of nonspecific effects of cortisone will be reported separately. No clinical data were given, but the cases studied were said to be of comparable severity: the dosage of cortisone (or of prednisone or prednisolone) administered and the duration of treatment were tabulated. Doses considered adequate because of their systemic effects on the disease process were found to be without influence on the development of verrucae on the cardiac valves; the fibrinous substance of the verrucae was organized slowly; the underlying connective tissue exhibited an important fibroblastic reaction; infiltration of inflammatory cells was lacking. Fibrinoid necrosis in the endocardial and myocardial connective tissue was found more frequently and more extensively in patients who had been treated with cortisone than in nontreated cases; the organization and reabsorption of the fibrinoid substance was slower in the treated cases. The number of Aschoff's bodies decreased as an effect of treatment; the architecture of the nodules was altered in that the follicular cells resembled fibroblasts and elaborate collagen; the protoplasm of some of the Aschoff cells became strongly basophilic; scarred nodules were prominent. The morphologic characteristics of the Aschoff cells seen in these treated cases support the opinion that they are of fibroblastic origin.

CALABRESI

ROENTGENOLOGY

Berrett, A., and McRae, D. L.: A Follow-Up study after Thorotrast Carotid Arteriography. Canad. M. A. J. **78**: 916 (June 15), 1958.

Possible toxic effects from Thorotrast administration were sought by studying 136 patients who had had carotid arteriograms for an average of 12½ years previously. The commonest effect, seen in 14 per cent, was fibrosis about the injection site (thorotrastoma), probably due to extravasation of the agent. This occurred despite the use of an open technic, but was usually small and asymptomatic. The only effect noted that was attributable to the prolonged systemic retention of radioactive material (thorium dioxide) was persistent roentgenologic density of the liver, spleen, and abdominal lymph nodes. Hemograms, chest and long-bone x-rays were available in a minority of patients and were nonrevealing. While more and longer follow-up studies are needed, at present it appears that Thorotrast toxicity is largely local in nature.

ROGERS

Tatelman, M.: The Angiographic Evaluation of Cerebral Atherosclerosis. Radiology **70**: 801 (June), 1958.

Two hundred consecutive patients with the clinical diagnosis of "stroke" or cerebral vascular accident admitted to the Cerebro Vascular Service of Detroit Memorial Hospital were studied angiographically. Angiograms were obtained by percutaneous injection of 8 to 10 ml. of 50 per cent Hypaque. From 2 to as many as 8 injections were given per patient with only 1 untoward reaction, an immediate fatality in a 60 year old woman who was critically ill. Autopsy in this case revealed neoplasm almost completely occluding the main pulmonary artery in the proximal portions of its branches. It appears that angiographic studies are quite safe in cerebral vascular disease. The combined clinical, neurologic and radiographic study on such patients has yielded much valuable information as to the etiology of symptoms. In addition to the more commonly described occlusions of the internal carotid and middle cerebral arteries, there is a relative frequency of occlusions of the vertebral-basilar artery system and of the anterior cerebral artery. Angiographic appearance of cerebral atherosclerosis without occlusion is described, and the importance of such findings is indicated. Complete occlusion of the internal carotid artery was encountered in 10.5 per cent of the 200 patients, of the anterior cerebral artery in 7.5 per cent, of the middle cerebral artery in 4.5 per cent, and of the vertebral-basilar arteries in 2.5 per cent. Significant narrowing of the internal carotid artery without complete occlusion was found in 10 per cent of this series. Fifty eight per cent showed some manifestation of atherosclerosis. A plea is made for visualizing the internal carotid artery down to its origin and for examining all vessels carefully for early signs of atherosclerosis.

KITCHELL

UNCOMMON FORMS OF HEART DISEASE

Friedman, S., and Ash, R.: Glycogen Storage Disease of the Heart. J. Pediat. **52**: 635 (June). 1958.

A detailed report on 5 infants who died with glycogen-storage disease is presented. These

children were all less than 3 months of age, were normal at birth and later developed upper respiratory tract infection, for which they were admitted to the hospital. In the course of observation they were discovered to have cardiac murmurs and cardiac enlargement. All developed muscular weakness and died a respiratory type of death. Autopsies were performed on all and in 2 muscle was submitted to Dr. Gerty Corey for analysis of glycogen and amylo 1-6 glucosidase. An extensive discussion of the electrocardiographic changes in these patients is presented. All tracings showed a sinus tachycardia, QRS complexes were of high amplitude, the P-R interval was not prolonged, and the Q-T interval was within the normal range. There was no axis deviation. A prominent R wave occurred on the right side of the chest and the QRS complexes were diphasic on the left side of the chest. Depressed S-T segments were found in the limb leads, negative T waves were present in all standard limb leads, and late inversion of the T and negative T waves on the left side of the chest were demonstrable in some of the tracings in the chest leads. An extensive pathologic report is presented in 1 patient.

HARVEY

Coates, E. O., Jr., and Drake, E. H.: Myxoma of the Right Atrium, with Variable Right-to-Left Shunt: Clinical and Physiologic Observations and Report of a Case with Successful Operative Removal. New England J. Med. **259:** 165 (July 24), 1958.

The case of a 50 year old woman in whom successful surgical removal of a myxoma of the right atrium was accomplished by open heart operation, using a pump oxygenator and a stopped heart is reported. Arterial-blood oxygen studies demonstrated a right-to-left shunt (through a patent foramen ovale) varying with change in body position, affording an important clue to the correct diagnosis. The findings of cardiac catheterization closely resembled those of Ebstein's syndrome. The definitive preoperative diagnosis of myxoma of the right atrium was established by angiocardiography, which demonstrated a large, lobulated filling defect in the right atrium. Since surgical cure of these lesions is now possible, the detection of intracardiac myxomas during life is important.

SAGALL

Hanley, T., Platts, M. M., Clifton, M., and Morris, T. L.: Heart Failure of the Hunchback. Quart. J. Med. **27:** 155 (April), 1958.

The clinical aspects, arterial blood gases and pulmonary function were described in 24 persons with severe kyphoscoliosis and compared with comparable observations in 10 patients with congestive failure and 14 without congestive failure. The signs in the cardiovascular system of patients with heart failure were similar to those in emphysema with anoxic cor pulmonale. Cardiac decompensation was often precipitated by exacerbation of respiratory infection. Clinical examination of the heart was usually not striking but the periphery showed undue warmth and flushing, full abrupt pulse and severe central cyanosis. Cardiac catheterization in 3 patients showed a moderate rise in pulmonary artery pressure. Severe kyphoscoliosis with or without cardiac failure produced great reduction in total lung capacity, vital capacity, maximum ventilation, and large residual air, but little evidence of impaired mixing or bronchial obstruction. Reduced arterial oxygen saturation and retention of carbon dioxide were present in 8 of 9 patients with true kyphoscoliotic heart disease but in only 2 of the 14 patients without heart failure and provided a clearer distinction between the 2 groups than any lung studies.

KURLAND

VASCULAR DISEASE

Clarke, E., and Harris, P.: Thrombosis of the Internal Carotid Artery. Lancet **1:** 1085 (May 24), 1958.

Thrombosis of the internal carotid artery may present the clinical picture of a space-occupying lesion. Five patients are presented in 4 of whom cerebral neoplasm was diagnosed and 1 cerebral abscess. The symptoms developed in 2 stages: first, the progressive or intermittent appearance of focal symptoms such as headache, convulsions, localized weakness, paresthesias or dysphagia and, second, the features of a space-occupying cerebral lesion. Radiography, lumbar puncture, electroencephalogram may not clarify the diagnosis. Certain differentiations can only be made by carotid angiography.

KURLAND

Robicsek, F., Sanger, P. W., Taylor, F. H., Magistro, R., and Foti, E.: Pathogenesis and Significance of Post-Stenotic Dilatation in Great Vessels. Ann. Surg. **147:** 835 (June), 1958.

On the basis of direct catheterization studies in man with pulmonic stenosis and aortic coarctation and hydrodynamic experimental observations, the authors offer an explanation for the pathogenesis of the hemodynamic paradox of post-stenotic dilatation. They point out that any change

that elevates the blood pressure or results in weakening the wall of a vessel at the circumscribed area might cause widening of the artery at that particular section. Since in the direct catheterization studies and in the model experiments localized increases in arterial blood pressure were not found in the poststenotic region, the theory of an elevation of lateral pressure below the level of the stenosis as the cause of the poststenotic dilatation can be eliminated. The hemodynamic studies indicated that the turbulent flow and, perhaps more important, cavitation with bubble formation in the poststenotic area were the factors causing severe injury to the vessel wall and dilatation. These factors acted more severely when the stenosis was abrupt rather than gradual. The poststenotic dilatation was an important differential diagnostic sign between stenosis involving a short or a long segment of a vessel. Poststenotic dilatation appears to be a favorable factor in blood circulation because it improves the blood flow below the level of the stenosis primarily enhancing the collateral flow and to a lesser degree the flow through the stenosis itself.

SAGALL

Chason, J. R.: Cerebral Infarction Secondary to Occlusive Arterial Disease. Radiology **70:** 811 (June), 1958.

Bland infarcts of the central nervous system are of 2 forms. The more common is the anemic type, where scant secondary hemorrhage is limited to the periphery of the area of necrosis; the less common is the hemorrhagic infarct, where blood fills all or most of the area destroyed. After the occurrence of an anemic infarct softening and liquiefaction gradually ensue. These changes begin probably within 6 hours, but the radiologist is most often confronted with such an infarct that is in the second or third week. At this time fluid accumulation and cell infiltration within the necrotic region can produce enlargement suggesting an expanding mass. Such progressive enlargement ends when the rate of removal of the necrotic material exceeds the rate of attraction of fluid and reactive cells, usually at the end of the third week. After this there is a gradual decrease in the size of the infarct accompanied by focal enlargement of the adjoining ventricular and subarachnoid spaces. In hemorrhagic infarction the story is similar to that of the anemic infarct except enlargement occurs earlier and is of greater degree and of longer duration. Vessels in the infarct rapidly undergo necrosis. Other vessels are subjected to a hypoxic state, which stimulates hypertrophy and hyperplasia of the endothelial cells. The lumens of these vessels are decreased in size and their effective use as collateral channels is impaired. Distal to the point of arterial obstruction, arterial or capillary emboli may form within the infarct and exert a detrimental influence upon the utilization of the vessels as part of the collateral circulation. The occluding thrombus or embolus may enlarge either distally or proximally and form a further serious threat to the availability of the existing channels.

KITCHELL

Meyer, J. S.: Theory and Rationale of Anticoagulant Therapy in Occlusive Cerebral Vascular Disease. Radiology **70:** 815 (June), 1958.

It is generally conceded that long-term anticoagulant therapy is of benefit in arteriosclerotic thrombosis and occlusion of the internal carotid and basilar arteries associated with intermittent ischemic episodes. Such therapy reduces the incidence or abolishes entirely the attacks but does not appear to affect significantly the course of severe infarction once it has occurred. The present report is concerned with an investigation of the action of anticoagulant drugs in experimental cerebral vascular disease. It appears that the mechanism of localized changes in cerebral vascular resistance following cerebral vascular occlusion is first a slowing of local flood flow with ischemic anoxia resulting in endothelial damage and localized loss of fluid constituents of the blood. This results in brain edema and localized hemoconcentration. Hemoconcentration is followed by increased adhesiveness of all formed elements of the blood and of the endothelium. The administration of heparin and Dicumarol prevents the adhesiveness of red cells, white cells, and platelets, and by this means prevents increased cerebral vascular resistance and promotes better collateral circulation.

KITCHELL

FRANCIS L. CHAMBERLAIN, M.D.

Francis L. Chamberlain, M.D., took office as President of the American Heart Association at the Association's recent Annual Meeting in San Francisco. Dr. Chamberlain, Associate Clinical Professor of Medicine, University of California School of Medicine, San Francisco, has been a leader for a decade in the Heart Association's program. A member of the national Board of Directors since 1952, Dr. Chamberlain was elected Vice-President for the 1956-57 term. He was Chairman of the Association's Policy Committee from 1955-57 and has served on the Research Study Committee of the Section on Clinical Cardiology. Dr. Chamberlain has also served as President of the California Heart Association and of the San Francisco Heart Association.

Born in Santa Cruz, Calif., Dr. Chamberlain received his undergraduate and medical degrees at the University of California and his M.Sc.D. at Columbia University in New York where he spent two years as resident in Medicine and Cardiology at Columbia Presbyterian Hospital, from 1935 to 37, and a year, from 1937-38, at Massachusetts General Hospital, Boston, as Cardiology Resident.

Dr. Chamberlain interned at Stanford University Hospital in 1933-34. He has been resident physician and Vice Chief of Staff at the University of California Hospital and has held appointments in many other hospitals in the San Francisco area. His training includes residencies, in 1936-37, under Dickinson Richards, M.D., and André Cournand, M.D., Nobel Prize winners for research in cardiac catheterization. Dr. Chamberlain was a member of the nation's first team to explore the heart's interior with a catheter, the procedure that has had such a profound effect on the development of today's brilliant epoch of heart surgery. In 1938-39, he was a Research Fellow in Cardiology and instructor in the Graduate School at Harvard University, and, from 1939 to 1946, was a full time teacher in charge of the Heart Clinic and Electrocardiography Laboratory at the University of California Medical School.

A member of the Board of Directors of the California State Medical Association, Dr. Chamberlain is also a member of the San Francisco Medical Society, the California Academy of Medicine, and the Western Society for Clinical Research.

AMERICAN HEART ASSOCIATION, INC.

44 East 23rd Street, New York 10, N. Y.

Telephone Gramercy 7-9170

LEADING ROLE BY PHYSICIANS WILL HELP HEART FUND DRIVE

The 1959 Heart Fund campaign throughout the month of February will be aided by hundreds of physicians who will again play a leading role in bringing to the American people the facts concerning cardiovascular diseases and the Heart Association's programs of research, education and community service.

With a final national 1958 Heart Fund total of $22,345,718, the 1959 national objective has been set at $24,000,000. More than half of the 1958 income received by the National Office of the Association will be allocated to research through grants-in-aid and the support of fellowships and investigatorships. In addition, a substantial portion of the funds retained by local Heart Associations will be channeled into scientific research. Approximately $35,400,000 has been allocated for research support by national, state and local Heart Associations since the Association became a national voluntary health agency 10 years ago.

Paul Dudley White, M.D., Boston, will serve as 1959 Honorary National Campaign Co-Chairman, with Mrs. Dwight D. Eisenhower serving as Honorary National Campaign Chairman. Both served in the same capacity for the 1958 Heart Fund. Charles Perry McCormick of Baltimore, an outstanding national business and civic leader, will again lead the drive as National Campaign Chairman.

On Heart Sunday, February 22, the most concentrated fund-raising effort will take place with an estimated million and a half volunteers representing 56 affiliates and more than 350 chapters calling on their neighbors throughout the nation for contributions.

ASSOCIATION'S COUNCILS ELECT NEW OFFICERS

New officers of the Association's seven Councils have been elected, as follows:

Council on Community Service and Education: Oglesby Paul, M.D., Chicago, Chairman; Herbert Pollack, M.D., New York, Vice Chairman; both re-elected for two year terms.

Council on Basic Science: Earl H. Wood, M.D., Rochester, Minn., Chairman; Gordon K. Moe, M.D., Syracuse, N.Y., Vice Chairman; Lysle L. Peterson, M.D., Philadelphia, Secretary.

Council on Circulation: Herbert Chasis, M.D., New York, Chairman; Kenneth Kohlstaedt, M.D., Indianapolis, Vice Chairman; Grace Roth, M.D., Rochester, Minn., Secretary.

Council on Rheumatic Fever and Congenital Heart Disease: Currier McEwen, M.D., New York, Chairman; James DuShane, M.D., Rochester, Minn., Vice Chairman.

Council on Cardiovascular Surgery: Frank Gerbode, M.D., San Francisco, Chairman; William W. L. Glenn, M.D., New Haven, Conn., Vice Chairman.

Council on Clinical Cardiology: Hugh H. Hussey, M.D., Washington, D.C., Chairman; Wright R. Adams, M.D., Chicago, Vice Chairman.

Council on High Blood Pressure Research: Maynard H. Murch, President; Frank E. Joseph, Vice-President; George E. Merrifield, Secretary; I. F. Freiberger, Treasurer; and Keith S. Grimson, Chairman, Medical Advisory Board, all of Cleveland.

TRANSACTIONS OF CONFERENCE ON CEREBROVASCULAR DISEASE OBTAINABLE IN BOOK FORM

The transactions of the Second Conference on Cerebrovascular Diseases held under the

sponsorship of the American Heart Association in Princeton, N.J., January 16-18, 1957, are now available in book form. Entitled "Cerebral Vascular Disease," the transactions were published for the Heart Association by Grune & Stratton.

Included in the transactions is a classification and outline of cerebrovascular disease. This is the report of an ad hoc committee established by the Advisory Council for the National Institute of Neurological Diseases and Blindness, U.S. Public Health Service.

Irving S. Wright, M.D., New York, acted as Chairman of the Conference and Clark H. Millikan, M.D., Rochester, Minn., as editor of the transactions. Cost of the volume is $4.00 a copy.

AHA CAREER INVESTIGATOR RECEIVES KIMBLE AWARD

Albert H. Coons, M.D., Visiting Professor of Bacteriology and Immunology at Harvard Medical School and a Career Investigator of the American Heart Association since 1953, has been presented with the eighth annual Kimble Methodology Research Award for outstanding contributions to improved procedures in the field of public health.

Dr. Coons was cited for developing a new technique for "labeling" antibodies with a fluorescent dye that glows under ultraviolet light. This method has made it possible to diagnose more quickly such infectious virus diseases as influenza, measles, mumps, etc. It has also proved a valuable tool for other scientific research.

The award, conferred on Dr. Coons at the Conference of State and Provincial Public Health Laboratory Directors of the American Public Health Association in St. Louis, includes an honorarium of $1,000 and an engraved plaque.

CARDIOVASCULAR PATHOLOGY SLIDES AVAILABLE ON LOAN

Sets of microscopic study slides on the subject of Cardiovascular Pathology have been prepared by the Armed Forces Institute of Pathology and now are available on a loan basis to physicians.

The slides, which come in sets of 100, show a varied selection of routine and rare lesions. Selective stains have been used where it was felt they were indicated or might have a more specific diagnosis. Scripts explaining the history and microscopic findings of each case are also in preparation to accompany the slides.

Sets of slides, 50 of which are available, may be borrowed by applying to the Scientific Director, American Registry of Pathology Armed Forces Institute of Pathology, 6825 Sixteenth Street, N.W., Washington 25, D.C.

A REQUEST OF THE PRACTICING PHYSICIAN

The Armed Forces Institute of Pathology is interested in receiving specimens of unusual cardiovascular diseases for its collection and for study. Before sending such material to the Institute, it is desirable to inquire how the specimens are to be preserved and packed.

SUBSCRIPTION RENEWALS

Renewals of subscriptions for 1959 of *Circulation* and *Circulation Research*, official professional journals of the American Heart Association, should be made directly through Grune & Stratton, Inc., 381 Fourth Avenue, New York 16, N.Y., publisher of the journals. Subscriptions should be renewed in this manner by either members or non-members of the Heart Association.

BOOKLET ON DIAGNOSIS IN REVISED EDITION

The Association's booklet, "Diagnosis of Congenital Cardiac Defects in General Practice," by Regina Gluck, M.D., New York, has been thoroughly revised and expanded and is now available to physicians through their local Heart Associations. The booklet describes common congenital cardiac defects and

presents briefly the physiology and clinical findings and the indications for surgery in defects that may be operable.

MEETINGS CALENDAR

January 22-24: American Federation for Clinical Research, Southern Section, New Orleans. Ellard M. Yow, Baylor University College of Medicine, Houston 25, Tex.

January 28-29: American Federation for Clinical Research, Western Section, Carmel, Calif. Richard J. Havel, University of California Medical Center, San Francisco 22, Calif.

March 17-19: National Health Council, Chicago. Philip E. Ryan, 1790 Broadway, New York 19, N.Y.

April 6-9: American Academy of General Practice, San Francisco. Mac F. Cahal, Volker B'lvd. at Brookside, Kansas City 12, Mo.

April 20-24: American College of Physicians, Chicago. E. R. Loveland, 4200 Pine Street, Philadelphia 4, Pa.

May 3-4: American Society for Clinical Investigation, Atlantic City. S. J. Farber, 550 First Avenue, New York 16, N.Y.

May 5-6: Association of American Physicians, Atlantic City. Paul B. Beeson, Yale University School of Medicine, New Haven 11, Conn.

May 26-29: American College of Cardiology, Philadelphia. Philip Reichert, 480 Park Avenue, New York 22, N.Y.

June 3-7: American College of Chest Physicians, Atlantic City. Murray Kornfeld, 112 E. Chestnut Street, Chicago 11, Ill.

June 8-12: American Medical Association, Atlantic City. F. J. L. Blasingame, 535 N. Dearborn Street, Chicago 10, Ill.

ABROAD

February 19-21: Central Surgical Association, Montreal, Canada. A. D. McLachlin, Victoria Hospital, London, Ontario, Canada.

July 27-30: Shaio Foundation Symposium on Cardiovascular Diseases, Bogota, Colombia. Alberto Vejarano-Laverde, 43-23 Carrera 13, Bogota-Colombia.

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why all the fuss over potassium?

Many physicians will recall when safe but potent organomercurials were first introduced. At the time there was considerable worry about possible potassium loss. Patients were instructed to take foods rich in this mineral, and not infrequently potassium supplements also were advised. After enough experience was gained, it became evident that only the exceptional case could lose enough potassium to be concerned about. And with oral organomercurial diuretics this was practically never a problem.

Why revive the subject now? Because clinical experience with nonmercurial diuretics indicates most of them have such a specific effect on potassium that with their use very real problems must be faced. Enough potassium loss can lead to digitalis toxicity or to a classical overt hypopotassemia. Since a fair percentage of cardiacs who receive diuretics are also digitalized, this excess potassium excretion is clinically serious. Clinical experience is still too limited with some nonmercurial diuretics to say just how often such loss will occur—but warnings already have been sounded by some clinical investigators as to the need for potassium supplementation.

Experience in many patients, for many years, demonstrates that potassium loss is never a problem when NEOHYDRIN® is the oral diuretic. And there is no refractoriness to this effective oral organomercurial.

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